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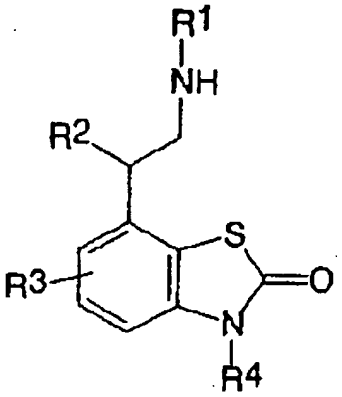
[Claim(s)]

1. Salt or Solvate Permitted on Following-type (I) Compound or Its Pharmacology :

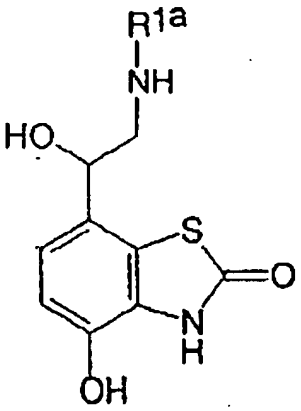


(I)

the inside of the above-mentioned formula, and R1 -- a hydrogen atom or one or more halogen atoms, and a hydroxyl group -- A cyano group, a nitro group, or the alkyl group of the carbon number 1-4 which may be replaced by the amino group, Express the alkenyl group of a carbon number 2-4, or the alkynyl group of a carbon number 2-4, and [R2 and R3] It may be the same or different and A hydrogen atom, a halogen atom, a hydroxyl group, A cyano group, a nitro group, an amino group or one or more halogen atoms, a hydroxyl group, Express the alkoxy group of the carbon number 1-4 which may be replaced by the cyano group, the nitro group, or the amino group, and [R4] Although the alkyl group of the carbon number 1-4 which may be replaced by a hydrogen atom or one or more halogen atoms, the hydroxyl group, the cyano group, the nitro group, or the amino group is expressed R1, R2, and R4 express a hydrogen atom, and R3 However, a hydrogen atom, When R1 expresses a methyl group, R2 and R4 express a hydrogen atom, when it expresses 4-hydroxyl group or 4-methoxy group, and R3 expresses 4-hydroxyl group, the case where R1 expresses n-propyl group and R2, R3, and R4 express a hydrogen atom is excluded.

R1 2. Hydrogen Atom or One or More Halogen Atoms, Hydroxyl Group, The alkyl group of the carbon number 1-4 which may be replaced by the cyano group, the nitro group, or the amino group is expressed. R2 expresses a hydroxyl group and R3 expresses a hydrogen atom, a halogen atom, a hydroxyl group, or the alkoxy group of the carbon number 1-4 which may be replaced with one or more halogen atoms. The compound according to claim 1 with which R4 expresses the alkyl group of the carbon number 1-4 which may be replaced with a hydrogen atom or one or more halogen atoms.

3. Salt or Solvate Permitted on Following-type (Ia) Compound or Its Pharmacology :



(I a)

(R1a expresses the alkyl group of the carbon number 1-4 which may be replaced by a hydrogen atom or one or more halogen atoms, the hydroxyl group, the cyano group, the nitro group, or the amino group among the above-mentioned formula) .

4. Compound according to claim 3 which is alkyl group of carbon number 1-4 by which R1a may be replaced with hydrogen atom or one or more halogen atoms.

5. Salt or solvate permitted on 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2 (3H)-ON or its pharmacology.

6. Medicinal composition which contains in any 1 clause of Claim 1 -5 salt or solvate which can be permitted on compound of description, or its pharmacology.

7. Medicinal composition according to claim 6 used for treatment of pulmonary problems chosen from bronchial asthma, asthmatic bronchitis, versicular emphysema, bronchitis, and acute bronchitis.

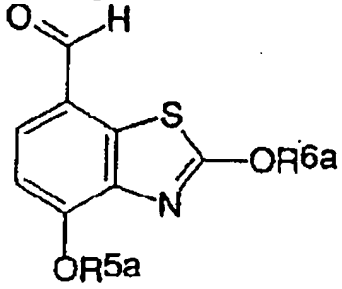
8. Medicinal composition according to claim 6 used for treatment of acute bronchial asthma.

9. Medicinal composition according to claim 6 which is form of epipastic for inhalation.

10. The medicinal composition according to claim 6 used for the treatment of the allergic disease chosen from allergic asthma, allergic coryza, allergic dermatitis, bronchial asthma, ******, itching, the allergic conjunctivits, and anaphylaxis.

11. The medicinal composition according to claim 6 used for the treatment of the inflammatory disease chosen from bronchitis and acute bronchitis.

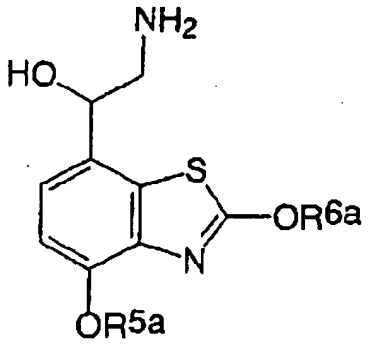
12. The respiratory tract or bronchodilator which contains in any 1 clause of Claim 1 -5 salt or solvate which can be permitted on the compound of a description, or its pharmacology.



(IIIa)

13. Following-type (III a) Compound :

([a / R5a and R6a may be the same or different, and] among the above-mentioned formula) The alkyl group of the carbon number 1-4 which may be replaced with a hydrogen atom and one or more halogen atoms, An acetyl group, a trifluoro acetyl group, benzoyl, a pivaloyl machine, a methoxycarbonyl group, a benzyl group, a PARAMETOKISHI benzyl group, a methoxymethyl machine, t-butyldimethylsilyl machine, or a triisopropyl silyl machine is expressed.



(Va)

14. Following-type (Va) Compound :

([a / R5a and R6a may be the same or different, and] among the above-mentioned formula) The alkyl group of the carbon number 1-4 which may be replaced with a hydrogen atom and one or more halogen atoms, An acetyl group, a trifluoro acetyl group, benzoyl, a pivaloyl machine, a methoxycarbonyl group, a benzyl group, a PARAMETOKISHI benzyl group, a methoxymethyl machine, t-butyldimethylsilyl machine, or a triisopropyl silyl machine is expressed.

15. Use of a compound given in any 1 clause of Claim 1 -5 for manufacture of the medicine for treatment of the pulmonary problems chosen from the group which consists of bronchial asthma, asthmatic bronchitis, versicular emphysema, bronchitis, and acute bronchitis.

16. Allergic Asthma, Allergic Coryza, Allergic Dermatitis, Use of a compound given in any 1 clause of Claim 1 -5 for manufacture of the medicine for treatment of the allergic disease chosen from bronchial asthma, urticaria, itching, the allergic conjunctivits, and the group that consists of anaphylaxis.

17. Use of a compound given in any 1 clause of Claim 1 -5 for manufacture of the medicine for treatment of the inflammatory disease chosen from the group which consists of bronchitis and acute bronchitis.

18. Include Medicating Mammals with Effective Dose of Salt Permitted on Compound Given in Any 1 Clause of Claim 1 -5, or Its Pharmacology, or Solvate with Carrier Permitted on Pharmacy. The cure for the pulmonary problems chosen from the group which consists of bronchial asthma, asthmatic bronchitis, versicular emphysema, bronchitis, and acute bronchitis.

19. Include Medicating Mammals with Effective Dose of Salt Permitted on Compound Given in Any 1 Clause of Claim 1 -5, or Its Pharmacology, or Solvate with Carrier Permitted on Pharmacy. The cure for the allergic disease chosen from allergic asthma, allergic coryza, allergic dermatitis, bronchial asthma, urticaria, itching, the allergic conjunctivits, and the group that consists of anaphylaxis.

20. The cure for the inflammatory disease chosen as any 1 clause of Claim 1 -5 from the group which consists of bronchitis and acute bronchitis including medicating the mammals with the effective dose of the salt permitted on the compound of a description, or its pharmacology, or solvate with the carrier permitted on pharmacy.

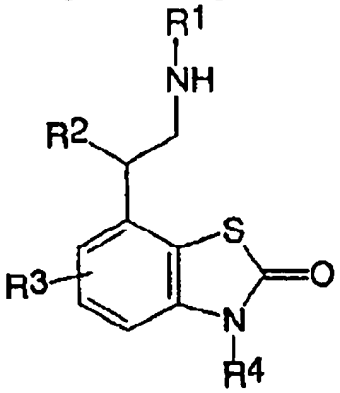
[Detailed Description of the Invention]

The benzothiazolone inductor which has alternative beta2 receptor agonist activity Background of invention Field of invention This invention relates to a pulmonary-problems treating agent, an allergic disease treating agent, and an inflammatory disease treating agent still in detail about the physic which contains the benzothiazolone inductor and it which stimulate beta2 receptor which exists in a respiratory tract smooth muscle as an active substance.

Background art Recent years, It is supposed that it is asthma the obstacle characterized from reversible airways obstruction, nonspecific airway hyperreactivity, and chronic respiratory tract inflammation (NHLBI/

WHO Workshop Report:Global Strategy for Asthma Management). and Preventation.National Institute of Health, National Heart, Lung, and and Blood Institute Publication Number 95-3659 (1995).
And although it is thought that many of chronic respiratory tract inflammation in bronchial asthma is allergic inflammation, about the formation of the inflammation, it is unknown.
Importance is attached to the medicine which has an anti-inflammatory operation as these therapeutic drugs, and the treatment using a steroid is made. However, there is a problem of side effects in a steroid (diagnosis, treatment, 81 volumes, 1185 - 1188 pages, 1993). On the other hand, allergic coryza is classified into I type allergy, and chemical mediators, such as histamine emitted from a mast cell, are considered to have played the important role. Although the antihistaminic etc. is used as these therapeutic drugs, the therapeutic drug which can fully be satisfied is not found out (the newest medicine, 49 volumes, 576 1994 [-591 or]).
Although allergic dermatitis is roughly divided into atopic dermatitis and allergic contact dermatitis, the therapeutic drug which can fully be satisfied is not found out.
Bronchial asthma is a disease characterized by reversible airway obstruction, and it is thought that airway obstruction is constituted by three factors of superfluous secretion ** of the twitch of 1 respiratory-tract smooth muscle, 2 oedema mucosal, and 3 respiratory-tract mucus. In this, it is known to the twitch of a respiratory tract smooth muscle that the beta receptor stimulant which is a bronchodilator is effective.
However, in order that these beta receptor stimulants may act also to the cardiac circulatory system, there is a problem of the use to ischemic heart disease, abnormal heart rhythm, and the hypertensive being restricted (diagnosis, treatment, 81 volumes, 1195 - 1204 pages). as opposed to beta1 receptor which exists in myocardium in order to solve this problem -- also depending -- being effective as an outstanding bronchodilator with little the compound which has big stimulus activity relatively to beta2 receptor which exists in a respiratory tract smooth muscle, i.e., an alternative beta2 receptor stimulant, and ******** is expected.
furthermore, Global Initiative for Asthma (Sohei Makino editorial-supervision: -- the international guideline of asthmatic management --) of the National Heart, Lung, and Blood Institute and the World Health Organization of the U.S. which is the guideline of asthmatic treatment Global strategy [of asthmatic management and prevention] and NHLBI/WHO workshop report (Japanese translation version) international medicine publication and 1995 recommend use of a short-time operation nature inhalation beta stimulant as a symptomatic emergency medicine aiming at an improvement of the transient subjective symptom in asthmatic treatment. receiving beta1 receptor also from the above thing -- also depending -- an alternative beta2 receptor stimulant of the short-time operation nature which has big activity relatively to beta2 receptor is desired.
On the other hand, by bronchial asthma, in the treatment at the time of a non-fit (asthma chronic), it is considered as one highest-value-for-expiratory-flow monitoring of an index, and the gradual cure based on the severity before treatment (it is classified into Steps 1-4, and severity becomes high at order) is performed. Moreover, the cure according to fit strength is performed in the cure at the time of a fit (acute asthma).
At Step 1, a short-acting beta2 receptor **** agent is specifically suitably inhaled as a cure at the time of a non-fit (asthma chronic), At Step 2-4, inhaling a short-acting beta2 receptor stimulant in a day if needed in 3 to 4 or less times /other than use, such as an inhalation anti-inflammatory agent and an oral beta2 receptor stimulant, is recommended. Moreover, as a cure at the time of a fit, the inhalation therapy of beta2 receptor stimulant is performed, and also the subcutaneous injection of epinephrine is performed.
However, in order that epinephrine may stimulate not only the beta2 receptor stimulus effect but the whole sympathetic nerve, when there is an obstacle of the cardiac circulatory system, there is a problem that it cannot be used. Furthermore, in order to stimulate similarly not only beta2 receptor but beta1 receptor, when a heart disease patient was medicated, there was a possibility that side effects might arise. From the above

thing, it is short-time operation nature, and high beta2 receptor stimulant of selectivity is expected.
However, the alternative beta2 receptor stimulant characterized by the above-mentioned short-time operation nature is not reported as far as this invention persons get to know.
For example, although isoproterenol (4-[hydroxy 2-[(1-isopropyl) amino] ethyl]-1, 2-dihydroxybenzene) is the beta receptor stimulant of short-time operation nature among the typical active substances of the existing medicine marketed The selectivity over beta2 receptor is low (Euro.J.Pharmacol. and vol.227,403-409(1992): Life Science, vol.52, 2145-2160 (1993)). Salbutamol ([2-t-butylamino 1-(4-hydroxy 3-hydroxy methylphenyl) ethanol hemi sulfate] although the selectivity over beta2 receptor is high) It is not short-time operation nature (Euro.J.Pharmacol., vol.227,403-409(1992);Life Science, vol.52, 2145-2160 (1993)).
. [moreover, FORUMO Taylor (N-[2-hydroxy 5-[(RS)-1-hydroxy 2-[(RS)-2-(4-methoxypheny)-1-methylethylamino] ethyl] phenyl] formamide hemi fumarate mono-hydrate)] It is long-acting although the selectivity over beta2 receptor is still higher as compared with salbutamol (Life Science, vol.52, 2145-2160 (1993)).
Moreover, Jounal of Medical Chemistry, vol.30, No.7, 1166-1176 (1987), U.S. Pat. No. 4554284, WO 92/No. 08708, WO 93/No. 23385, The benzothiazolone inductor is indicated by WO 93/No. 24473, WO 95/No. 04047, WO 95/No. 25104, WO 97/No. 10227, WO 97/No. 23470, and U.S. Pat. No. 5648370.
Schema of invention This invention persons have alternative beta2 receptor stimulus activity, and looked for the compound with short reaction time. As a result, **** reaction time is [in which the benzothiazolone inductor of a certain kind which has the ethanolamine structure replaced by the low-grade alkyl group in the 7th place stimulates alternatively beta2 receptor which exists in a respiratory tract smooth muscle] short, The TNF-alpha production from a Homo sapiens mast cell is controlled [inhibiting the degranulation from a Homo sapiens mast cell,], It found out inhibiting the skin reaction by passive cutaneous anaphylaxis and histamine in loosening the bronchial tube of a mouse and a guinea pig in in vivo, a mouse, and a rat etc. This invention is based on this knowledge.
Therefore, this invention sets it as the purpose to offer the new compound which stimulates beta2 receptor alternatively for a short time. Moreover, this invention sets it as that purpose to offer the medicinal composition containing this new compound.
And the benzothiazolone inductor by this invention is those salt and solvate which are permitted on the compound and pharmacology which are expressed with the following type (I). :



(I)

the inside of the above-mentioned formula, and R1 -- a hydrogen atom or one or more halogen atoms, and a hydroxyl group -- A cyano group, a nitro group, or the alkyl group of the carbon number 1-4 which may be replaced by the amino group, Express the alkenyl group of a carbon number 2-4, or the alkynyl group of a carbon number 2-4, and [R2 and R3] It may be the same or different and A hydrogen atom, a halogen atom, a hydroxyl group, A cyano group, a nitro group, an amino group or one or more halogen atoms, a hydroxyl group, Express the alkoxy group of the carbon number 1-4 which may be replaced by the cyano group, the

nitro group, or the amino group, and [R4] Although the alkyl group of the carbon number 1-4 which may be replaced by a hydrogen atom or one or more halogen atoms, the hydroxyl group, the cyano group, the nitro group, or the amino group is expressed R1, R2, and R4 express a hydrogen atom, and R3 However, a hydrogen atom, When R1 expresses a methyl group, R2 and R4 express a hydrogen atom, when it expresses 4-hydroxyl group or 4-methoxy group, and R3 expresses 4-hydroxyl group, the case where R1 expresses n-propyl group and R2, R3, and R4 express a hydrogen atom is excluded.
moreover, the thing containing salt or solvate which can permit the medicinal composition by this invention on the compound of a formula (I), or its pharmacology -- it comes out.
The compound by this invention has the drug effect which was excellent compared with the conventional medicine, further, does not have fear of the side effects to a heart disease patient, and is excellent also in quick action. Therefore, according to this invention, pulmonary problems safe for a human body, an inflammatory disease, and/or an allergic disease treating agent are offered.
Brief explanation of the drawings Drawing 1 shows 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 of sponge origin, and the proton magnetic resonance spectrum (inside of 500MHz and heavy water) of 3-benzothiazole 2(3H)-ON (example 1).
Drawing 2 is 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 of sponge origin, and the 3-benzothiazole 2 (3H). - It turns on (example 1).
A ** 13C magnetic resonance spectrum (inside of 500MHz and heavy water) is shown.
Drawing 3 expresses the extraction guinea pig bronchial tube relaxation operation with an application-concerned compound. - : the compound of an example 2, **:salbutamol, **:FORUMO Taylor, O: isoproterenol.
Drawing 4 expresses the retention time of an extraction guinea pig bronchial tube relaxation operation of an application-concerned compound. - : the compound of an example 2, **:salbutamol, **:FORUMO Taylor, O: isoproterenol.
Drawing 5 expresses the effect of an application-concerned compound over the bronchoconstrictive action by the acetylcholine of the bottom mouse of anesthesia. - : : (30microg/(kg)) control (prescribing [no] a medicine for the patient), the compound (1microg/(kg)) of the **:example 2, the compound (10microg/(kg)) of the **:example 2, the compound of the O:example 2
Drawing 6 expresses the effect of an application-concerned compound (example 2) over the degranulation from a Homo sapiens mast cell.
Drawing 7 expresses the effect of an application-concerned compound over the TNF-alpha production from a Homo sapiens mast cell.
Drawing 8 is 4-hydroxy 7-[1. - (1-hydroxy 2-methylamino)
The outline of the synthetic pathway of ethyl]-1 and 3-benzothiazole 2(3H)-ON is shown.
Concrete explanation of invention Compound of a formula (I) In this Description, an alkyl group, an alkenyl group, an alkynyl group, and the alkoxy group can be a straight chain or branched chain.
In this Description, the methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, and s-butyl group are mentioned as an example of the alkyl group of a carbon number 1-4 which R1, R4, and R1a express.
In this Description, vinyl (ethenyl), 1-propenyl, allyl (2-propenyl), isopropenyl, 2-butenyl and 1, and 3-swine dienyl machine is mentioned as an example of the alkenyl group of a carbon number 2-4 which R1 expresses.
In this Description, the ethynyl, 1-propynyl, and 2-propynyl group are mentioned as an example of the alkynyl group of a carbon number 2-4 which R1 expresses.
In this Description, methoxy and ethoxy **n-propoxy, i-propoxy, n-butoxy, i-butoxy, t-butoxy, and an s-

butoxy machine are mentioned as an example of the alkoxy group of a carbon number 1-4 which R2 and R3 express.

[one or more hydrogen atoms of an alkyl group, an alkenyl group, an alkynyl group, and an alkoxy group] A.halogen atom, a hydroxyl group, a cyano group, a nitro group, or an amino group (preferably) It may be replaced by the halogen atom and difluoromethyl, trifluoromethyl, 2, 2, and 2-trifluoroethyl and a trifluoro methoxy group are mentioned as an example of the replaced alkyl group, an alkenyl group, an alkynyl group, and an alkoxy group.

In this Description, a halogen atom shall mean a fluoride atom, a chlorine atom, a bromine atom, and an iodine atom.

In a formula (I), preferably R1 A hydrogen atom or one or more halogen atoms, The alkyl group of the carbon number 1-4 which may be replaced by the hydroxyl group, the cyano group, the nitro group, or the amino group is expressed, and the alkyl group (especially methyl group) of the carbon number 1-4 which may be replaced with a hydrogen atom or one or more halogen atoms is expressed still more preferably.

Moreover, in a general formula (I), R2 expresses a hydroxyl group preferably.

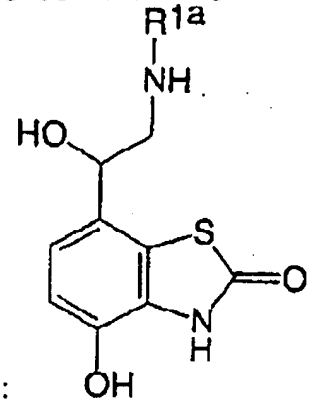
In a formula (I), R3 expresses preferably the alkoxy group of the carbon number 1-4 which may be replaced with a hydrogen atom or one or more halogen atoms, and expresses a hydroxyl group or a methoxy group still more preferably. R3 can be preferably located in the 4th place of a benzothiazolone ring.

In a formula (I), R4 expresses preferably the alkyl group of the carbon number 1-4 which may be replaced with a hydrogen atom or one or more halogen atoms, and is a hydrogen atom still more preferably.

Although an optical isomer may exist in the compound by this invention, any of the isomers and those mixtures are also included by this invention.

As a desirable compound group of the compound by this invention R1 A hydrogen atom or one or more halogen atoms, a hydroxyl group, a cyano group, The alkyl group of the carbon number 1-4 which may be replaced by the nitro group or the amino group is expressed. R2 expresses a hydroxyl group and R3 expresses a hydrogen atom, a halogen atom, a hydroxyl group, or the alkoxy group of the carbon number 1-4 which may be replaced with one or more halogen atoms. The compound of a formula (I) with which R4 expresses the alkyl group of the carbon number 1-4 which may be replaced with a hydrogen atom or one or more halogen atoms is mentioned.

A following-type (Ia) compound is mentioned as a still more desirable compound of the compound by this invention. :



(Ia)

(R1a expresses the alkyl group of the carbon number 1-4 which may be replaced by a hydrogen atom or one or more halogen atoms, the hydroxyl group, the cyano group, the nitro group, or the amino group among the above-mentioned formula) .

It is the alkyl group (especially methyl group) of the carbon number 1-4 by which R1a may be preferably replaced with a hydrogen atom or one or more halogen atoms in the formula (Ia).

******

As most desirable compound of the compound by this invention, 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2(3H)-ON is mentioned.

The compound by this invention can be made into the salt permitted on the pharmacology. The nontoxic salt permitted on pharmacology is mentioned as such salt. Salt of the alkali metal or alkaline earth metal like sodium salt, potassium salt, or calcium salt as a desirable example, Hydrofluoric-acid salt, a hydrochloride, the hydrobromate, halide acid salt like hydrogen iodide acid chloride, Inorganic-acid salt, such as a nitrate, perchlorate, a sulphate, and an orthophosphate, methanesulfon acid chloride, Trifluoro methanesulfon acid chloride, low-grade alkyl sulfonate like ethane-sulfonic-acid salt, Benzenesulfonic acid salt, aryl sulfonate like p-toluenesulfonic acid salt, Amino acid salt like organic acid salt like fumaric acid chloride, the succinate, citrate, a tartrate, an oxalate, maleate, acetic acid, a malic acid, lactic acid, and ascorbic acid and glutamate, and aspartic acid salt etc. is mentioned.

The compound by this invention can be made into solvate (for example, hydrate) again.

Manufacture of the compound of a formula (I) Extraction operation can isolate and refine the compound of the formula (Ia) which is the typical compound of the compound of a formula (I) from the sponge which lives all over the sea. Specifically sponge is crushed using a blender etc., a crush thing is freeze-dried, and the solvent mixture of methanol, ethanol, acetone or methanol, and chloroform etc. extracts this. Operation of lyophilization may be omitted and the crush thing of sponge may be given to extraction operation as it is. In extraction operation, you may enforce the countercurrent distribution method by a suitable solvent. Subsequently, after applying the above-mentioned extract to a suitable sorbent (for example, alumina, a silica gel, activated carbon, ion-exchange resin, "DAIA ion HP20" (made by Mitsubishi Chemical)) etc. and making the purpose compound adsorb, it is eluted with a suitable solvent. The compound by this invention can be obtained by carrying out vacuum concentration hardening by drying of this.

In order to refine the compound by this invention further, the number of necessity times may combine gel filtration technique, a high speed liquid chromatography, etc. with the above-mentioned extraction and adsorbing operation if needed. Specifically, the high speed liquid chromatography by the column chromatography by gel filtration agents, such as sorbents, such as a silica gel, and "sephadex LH-20" (Pharmacia manufacture), a "YMC pack" (made by a mountain village science company), etc. is further combinable with a countercurrent distribution method.

The compound of the formula (Ia) which is the representation compound of the compound of a formula (I) is also compoundable according to the scheme of a description to drawing 8 .

The compound of the formula in a scheme (II) can leave commercial 2-methoxy 5-methylphenyl thiourea, for example, and can be compounded. Moreover, the compound of a formula (II) follows a procedure given in Journal of Medicinal Chemistry, vol.30, pp 1166-1176 (1987), and JP,S61-68746,A, for example. It is also compoundable from 2-methoxy 5-methylaniline (these articles are used as some application-concerned Descriptions by quoting).

The process in a scheme (i) is a process which oxidizes the compound shown by a formula (II).

The compound shown by a formula (II) in a suitable solvent (for example, polar solvents, such as acetonitrile, methanol, and ethanol, preferably methanol) With cerium ammonium night REITO, it is 40-60 degrees C preferably, and 0 degree C - 100 degrees C of compounds preferably shown by a formula (III) by making it react for for 15 minutes to 1 hour for for 5 minutes to 6 hours are obtained.

Here, R5 and R6 express the blocking group of a hydroxyl group among a formula (II), and R7 expresses the alkyl group of a carbon number 1-4. as the blocking group of a hydroxyl group -- for example, an ester system blocking group (for example, an acetyl group --) A trifluoro acetyl group, benzoyl, a pivaloyl machine, a methoxycarbonyl group, etc., Ether system blocking groups (for example, a benzyl group, a

PARAMETOKISHI benzyl group, a methoxymethyl machine, the alkyl group of a carbon number 1-4, etc.) and silyl system blocking groups (for example, t-butyldimethylsilyl machine, a triisopropyl silyl machine, etc.) are mentioned.

A process (ii) is a process which changes into cyanohydrin the formyl group of the compound shown by a formula (III). The compound shown by a formula (III) in an inert solvent (for example, halogenated hydrocarbon, such as a methylene chloride, chloroform, and a carbon tetrachloride, preferably methylene chloride) A trimethylsilyl cyanide, suitable Lewis acid, and the compound that is room temperature preferably and is preferably indicated to be zinc iodide by a formula (IV) by making it react for [for / 10 minutes / -] 15 minutes 0 degree C - 100 degrees C for for 5 minutes to 6 hours are obtained.

A process (iii) is a process which returns the cyano group of the compound shown by a formula (IV). the compound shown by a formula (IV) -- a reducing agent suitable in a suitable solvent (for example, ether, such as tetrahydrofuran and dioxane) -- [diisobutyl aluminum hydroxide / lithium hydride aluminum,] preferably - It is -10 degrees C - 10 degrees C preferably, and obtain 20 degrees C - 100 degrees C of compounds preferably shown by a formula (V) by making it react for [for / 10 minutes / -] 15 minutes for for 5 minutes to 12 hours.

A process (iv) is a process which protects the hydroxyl group of the compound shown by a formula (V). For example, when X is t-butyldimethylsilyl machine, the compound shown by a formula (V) in a suitable inert solvent (for example, halogenated hydrocarbon, such as a methylene chloride, chloroform, and a carbon tetrachloride) Trifluoro methanesulfonic acid t-butyldimethylsilyl, a base (for example, [a pyridine, a dimethylamino pyridine lutidine, etc.] preferably) lutidine -being 0 degree C - 5 degrees C preferably, and making 10 degrees C - 50 degrees C react preferably from 10 minutes for 0.5 hour - 1.5 hours for 12 hours -- a formula (VI)

It comes out and the compound shown is obtained.

A process (v) is a process which protects the amino group of the compound shown by a formula (VI). For example, in the case of an acetyl group, a trifluoro acetyl group, and an acyl group like benzoyl, Y the compound shown by a formula (VI) [with the inside of a suitable inert solvent, or a non-solvent] [carboxylic anhydride / carboxylic acid and a suitable binder (for example, DDC), a carboxylate salt ghost,] under a base and the existence which is a pyridine preferably - It is 0 degree C - 5 degrees C preferably, and obtain 10 degrees C - 60 degrees C of compounds preferably shown by a formula (VII) by making it react for 12 hours for [for / 10 minutes / -] 30 minutes after for 5 minutes.

A process (vi) is a process which introduces R1a (the radical of the same content as the above is expressed) into the compound shown by a formula (VII). When R1a is an alkyl group, the compound shown by a formula (VII) in a suitable solvent (for example, N,N-dimethylformamide) [alkyl halide] under existence of a base (preferably sodium hydride, such as for example, sodium hydride, potassium hydride, potassium carbonate, sodium carbonate, etc.) - It is -10 degree-C-10 preferably and obtain 20 degrees C - 100 degrees C of compounds shown by a formula (VIII) for for 5 minutes to 12 hours by making it react for [for / 10 minutes / -] 20 minutes preferably.

Probably, it will be clear to a person skilled in the art that R1a can compound the compound of the formula (VIII) which are radicals other than an alkyl group according to the above-mentioned procedure.

A process (vii) is a process which performs deprotection of the compound shown by a formula (VIII). For example, when X is t-butyldimethylsilyl machine and Y is a trifluoro acetyl group, the compound shown by a formula (VIII) in a suitable solvent (ether, such as tetrahydrofuran and dioxane) suitable acid or fluoridation tetrabutylammonium -- [tetrabutylammonium / fluoridation] preferably - It is -10 degrees C - 10 degrees C preferably, and exclude 10 degrees C - 60 degrees C of t-butyldimethylsilyl machines for for 10 minutes to 12 hours by making it react preferably for for 10 minutes to 1 hour. then, alcohols, such as

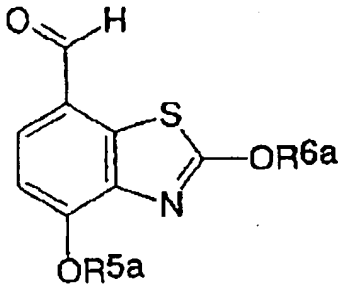
methanol and ethanol, -- in methanol preferably Sodium alcoholate, potassium alkoxide, and the compound preferably shown by a formula (IX) 0 degree C - 100 degrees C with sodium methoxide 5 degrees C - 40-degree-C **, and by making it react for [for / 10 minutes / -] 30 minutes preferably for for 10 minutes to 12 hours are obtained.

A process (viii) is a process which performs deprotection of the compound shown by a formula (IX). [the compound shown by a formula (IX)] in the suitable solvent (for example, halogenated hydrocarbon, such as a methylene chloride, chloroform, a carbon tetrachloride, and a benzene chloride, acetonitrile, preferably acetonitrile) which does not check a reaction suitable acid, Lewis acid, and sodium thio methoxide -- desirable -- boron tribromide -it is 5 degrees C - 40 degrees C preferably, and 20 degrees C - 100 degrees C of compounds preferably shown by a formula (I) by making it react for 12 hours - 40 hours for 1 hour - 72 hours are obtained.

In addition, probably, in the above-mentioned synthetic process, it will be clear to a person skilled in the art that a functional group may be protected by a suitable blocking group so that a synthetic order may be determined that side reaction will not arise in the functional group which does not participate in a reaction and the reaction which is not desirable may not advance. Moreover, probably, it will be clear to a person skilled in the art that the compound of the formula (I) which is not contained in a formula (Ia) can be obtained by adding an alteration to starting material etc.

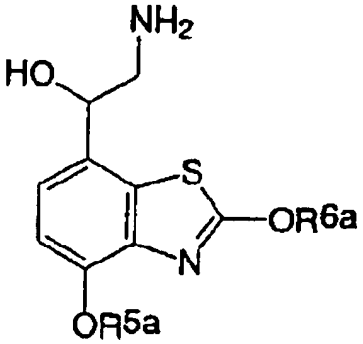
The acid addition salt of the compound of a formula (I) can be manufactured by adding equivalent or excess quantity of acid in the solvent liquid of the compound concerned which dissolved into suitable organic solvents, such as the well-known procedure, for example, methanol, ethanol, and 2-propanol.

The intermediate product of a formula (III) and a formula (V) is a new compound among the scheme of drawing 8 . Therefore, according to this invention, the compound of the following type (IIIa) and a formula



(IIIa)

(Va) is offered. :



(Va)

([a / R5a and R6a may be the same or different, and] among the above-mentioned formula) The alkyl group of the carbon number 1-4 which may be replaced with a hydrogen atom and one or more halogen atoms, An acetyl group, a trifluoro acetyl group, benzoyl, a pivaloyl machine, a methoxycarbonyl group, a benzyl group, a PARAMETOKISHI benzyl group, a methoxymethyl machine, t-butyldimethylsilyl machine, or a triisopropyl silyl machine is expressed.

The compound of the above-mentioned formula (IIIa) and a formula (Va) is useful as an intermediate

product at the time of manufacturing the compound of a formula (Ia).
the use/medicinal composition of a compound the compound by this invention receives beta1 receptor -- also depending -- it has relative very big activity to beta2 receptor. That is, the compound by this invention has alternative beta2 receptor stimulus activity. Moreover, the compound by this invention loosens the extraction bronchial tube organization of a guinea pig by low concentration very much. Furthermore, if a mouse is actually medicated with the compound by this invention, a very strong bronchodilator action will be accepted.
Therefore, the compound by this invention is useful for the treatment of pulmonary problems like bronchial asthma (for example, acute bronchial asthma, chronic bronchial asthma), asthmatic bronchitis, versicular emphysema, bronchitis, and acute bronchitis. It is expected that it will be a pulmonary-problems treating agent without side effects, such as heart rate potentiation, since the compound by this invention has very strong alternative beta2 receptor stimulus activity. In this Description, the reversibility respiratory tract obstruction shall be included in pulmonary problems, and a respiratory tract extension agent and a bronchodilator shall be contained in the physic for pulmonary-problems treatment.
The compound by this invention has beta2 receptor stimulus activity with reaction time short again very. Therefore, especially the compound by this invention is useful for the treatment of the disease (for example, acute bronchial asthma) which requires emergency nature among pulmonary problems.
Moreover, the compound by this invention controls discharge of the degranulation from a Homo sapiens mast cell, i.e., the chemical mediator from a mast cell, (chemical mediator). Discharge of a chemical mediator Allergic asthma (bronchial asthma is included), allergic coryza, Allergic dermatitis (for example, atopic dermatitis and allergic contact dermatitis), An allergic disease like urticaria, itching, the allergic conjunctivits, and anaphylaxis, Causing an inflammatory disease like bronchitis and acute bronchitis is known (**, **, 44 No. 12, 1240 - 1247 pages, and 1255 - 1260 pages (1996); the newest medicine, 49 volumes (special issue), 102 - 122 pages (1994)). The compound by this invention controls the TNF-alpha production from a Homo sapiens mast cell again. TNF-alpha Allergic asthma (bronchial asthma is included), allergic coryza, Causing allergic dermatitis (for example, atopic dermatitis and allergic contact dermatitis), urticaria, itching, allergosis like the allergic conjunctivits, and an inflammatory disease like bronchitis and acute bronchitis is known (above-shown literature). Furthermore, the compound by this invention inhibited the allergic response by passive cutaneous anaphylaxis and histamine in the mouse and the rat.
Therefore, the compound by this invention is useful for the treatment of an allergic disease or an inflammatory disease. In addition, an allergic disease may mean a part of inflammatory disease, and an inflammatory disease may mean a part of allergosis.
According to this invention, the medicinal composition used for the treatment of the above-mentioned disease is offered.
[the compound by this invention / pertinent arbitrary routes of administration and a concrete target] [in the case of animals other than Homo sapiens / procedures, such as intravascular medication in intraperitoneal injection, hypodermic administration, a vein, or an artery, and partial medication by injection,] Moreover, in the case of Homo sapiens, it is possible to prescribe a medicine for the patient by medication to intravenous administration, intraarterial administration, the partial medication by injection, the abdominal cavity, and the thorax, internal use, inhalation medication, hypodermic administration, intramuscular administration, sublingual administration, percutaneous absorption, or rectum medication.
Intravenous administration or inhalation medication is desirable.
As an inhalation instrument used for inhalation, for example A jet type nebulizer, There are an ultrasonic nebulizer, HFV (high frequency vibration), IPPB (intermittent positive pressure breathing), quantum spraying type vapor, and spin HERA. From a viewpoint of the instantaneous effect, portability, and simple

nature, a fixed quantity of spraying type vapor is used preferably (reference: the volume on Chiba child bronchial asthma inhalation-therapy study group, an inhalation-therapy manual, 18 - 23 pages, 1992). Although the compound by this invention may be prescribed for the patient as it is, it is desirable that a prescription is written as a medicinal composition and a medicine is prescribed for the patient with the carrier permitted on pharmacology. Although the formula of a medicinal composition may be suitably determined in consideration of a medication method and the medication purpose, it can be prescribed for the patient with the form of the epipastic (epipastic for inhalation), the injection, the suspension, a tablet, the pellet, the powder, the capsule, the salve, cream pharmaceuticals, etc., for example. The injection or the vapor is desirable.

As a solvent, as a solubilizer ethanol and a polysorbate agent, for example for water, a physiological saline, etc., for example as an excipient For example, milk sugar, a starch, a crystalline cellulose, a mannitol, a maltose, dibasic calcium phosphate, light anhydrous silicic acid, calcium carbonate, etc. as a binder For example, a starch, a polyvinylpyrrolidone, hydroxypropylcellulose, the ethylcellulose, carboxymethyl cellulose, gum arabic, etc. as disintegrator For example, the magnesium stearate, talc, hydrogenated oil, etc. can be used, for example for milk sugar, a mannitol, a maltose, polysorbates, macro Gaul, polyoxyethylene hydrogenated castor oil, etc. as a stabilizer. Moreover, glycerin, dimethylacetamide, 70% sodium lactate, a surface-active agent, and a basic substance (for example, the ethylenediamine, ethanolamine, the sodium carbonate, arginine, meglumine, tris aminomethane) can also be added if needed. It can manufacture to drug designs, such as the injection, a tablet, pellet, vapor or aerosols, and capsule, using these ingredients.

In fixed quantity, in the spraying type vapor, the medicine of this invention can be prescribed as solution or a water-soluble suspension, and can be prescribed for the patient. For example, the aerosol spray formula suspended in a discharge agent, for example, compressed air, compression carbon dioxide, or a fron system propeller ton together with one sort or two sorts or more of stabilizers depending on the case can also use a medicine again. As an example of fron system pro PURATON, chlorofluorocarbon (CFC-11, CFC-12, and CFC-114), There are hydrochlorofluorocarbon (HCFC-123, HCFC-124, and HCFC-141), a hydrofluorocarbon (HCFC-125 and HFC-134a), etc. Moreover, the medicine of this invention can take the form of the powder mixture of a suitable carrier like a dry type powder composition, for example, an active ingredient, and a lactose about medication by inhalation or injection. This powder composition can be given, for example with the unit medication form under a capsule, a cartridge, or blister packaging. [forms / these / powder] with the help of an inhaler like a rotor HEIRA (Rotahaler) inhaler (Glaxo Group brand name) Or in the case of blister packaging, a medicine can be prescribed for the patient with a desk HEIRA (Diskhaler) inhaler (Glaxo Group brand name). Moreover, by the prescribing [for the patient]-a medicine method using a nebulizer and an inhalation instrument, the particle size of the medicine or the powder composition should be 100 micrometers or less, and it is desirable to be sprayed so that it may be set to 25 micrometers from 0.5 micrometer.

The dose of a compound is set that the total dose does not exceed a fixed quantity, when various situations are taken into consideration and prescribed for the patient continuously or intermittently. Specifically, they are about 0.01-500mg of adult 1 Japanese hits. With the spraying type vapor, a fixed quantity is adjusted so that it may become 0.01-0.5ml of 1 spraying, and it is about 0.001-10mg per 1 spraying. The exact dose used is determined by a clinical doctor or the veterinarian depending on a route of administration, a medication method and a patient's age, weight, and condition.

In this Description, it shall be used with "treatment" in the meaning including prevention.

According to this invention, the cure for these diseases including medicating animals other than the Homo sapiens suffered from pulmonary problems, an inflammatory disease, and/or an allergic disease or Homo sapiens with salt or solvate which can be permitted on the compound of an effective dose of formulas (I) or

its pharmacology is offered. The medication method of the compound of a formula (I) can be performed according to the above-mentioned description.

. Although the following example explains this invention still in detail, this invention is not limited to these.

Example 1 4-hydroxy 7-[1-(1-hydroxy 2-substitution amino) ethyl]-1, isolation and refining of 3-benzothiazole 2(3H)-ON 8kg of sponge (Dysidea sp.) extracted around April to June was freeze-dried after pulverization in the sea near Okinawa using the blender. 935g powder was further obtained for the freeze-dried sponge using the blender. It is methylene chloride methanol (1:1) about the powder-ized sponge. It extracted 3 times using **********. After condensing the extractant, it was made to dissolve in 3l. of ethyl acetate, and twice operation of the distribution chromatography was carried out using the distilled water of capacity 1.5 times. A total of the obtained 8l. water fraction was condensed, and about 200g concentrate was obtained. the silica gel column (the Merck Co. make --) beforehand equilibrated with methylene chloride methanol (15:1) This concentrate is made to stick to the column (7cm phix50cm) of a silica gel 60. 4l. was further eluted [methanol / (15:1) / methylene chloride / water / (3:1:0. 1) / methylene chloride methanol] at 3l. in methylene chloride methanol water (1:1:0. 1) in 2l. and the next. The activity fraction was condensed and the 80g concentrate was obtained.

40g of obtained concentrates were dissolved with methanol 20%, and this concentrate was made to stick to the column (100ml) of activated carbon. It is 70% acetone (0.4% trifluoroacetic acid) to 300ml and the next after washing and about 70% acetone with 300ml of 20% methanol.

It was eluted at 600ml. After carrying out concentration hardening by drying of the activity fraction, fractionation was carried out by making the obtained concentrate into an eluent with the liquid high speed chromatography using the ODS column (YMC CO., LTD., SH-343-7) as 20% methanol 80%20mM potassium phosphate buffer solution (pH 7.0) and a column.

After carrying out concentration hardening by drying of the activity fraction, fractionation was further carried out with the same liquid high speed chromatography, using 10% methanol 90%20mM potassium phosphate buffer solution (pH 7.0) as an eluent. After carrying out concentration hardening by drying of the activity fraction, this concentrate was made to stick to the column (1.2cm phix20cm) of the silica gel column (the Merck Co. make, silica gel 60) beforehand equilibrated with methylene chloride methanol water (3:1:0. 1), and it was eluted with the same solvent as having used for equilibration.

the alumina column (the Merck Co. make --) which equilibrated the obtained rough refining things beforehand with methylene chloride methanol water (6:1:0. 1 or 2% acetic acid) after carrying out concentration hardening by drying of the activity fraction After making it stick to the column (1.0cm phix20cm) of aluminum oxide 60, It was eluted with the same solvent as having used for equilibration, and 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2(3H)-ON acetate (4.8mg) was obtained. The result of a proton (drawing 1) and the nuclear magnetic resonance spectrum of 13C (drawing 2), And it checked that this compound was 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2(3H)-ON from the result of the high resolution mass spectrum.

^{1}H-NMR(D_2O)

2.71(s, 3H, $NHCH_3$), 3.26(m, 2H, CH_2 $NHCH_3$), 5.03 (dd, J=4.3Hz, 8.5Hz, 1H, CH $OHNHCH_3$), 6.8(d, J=8.5Hz, 1H, ArH-5), 7.0(d, J=8.5Hz, 1H, ArH-6)

MS ; [M+H] =241、 $[\alpha]_d^{26}=-10.0°$

Synthesis of example 2 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2(3H)-ON
The outline of synthesis of a title compound is as being shown in drawing 8 .

(1) Synthesis of 2, the 4-dimethoxy 7-methyl 1, and 3-benzothiazole (II) 2-methoxy 5-methylphenyl thiourea (Lancaster; #12101) (3.0g) is dissolved in chloroform (70ml). The chloroform solution (10ml) of bromine (4.9g) was dropped under ice-cooling. The heating reflux was carried out for 40 more minutes **** during 30 minutes, and after that at room temperature after the end of dropping. After cooling to room temperature, the ** collection of the depositing crystal was carried out, and acetone washed. The obtained white crystal is dissolved in hot water (180ml), after cooling, using ammonia water, it adjusted to pH 10 and the white crystal was deposited. The ** collection carried out this crystal and reduced pressure drying was carried out. The obtained crystal was dissolved in phosphoric acid (80ml), and sodium nitrite (2.22g) solution (8ml) was dropped at -15 degrees C under cooling. It ****(ed) for 90 more minutes at -15 degree C after the end of dropping, and the purple suspension was obtained. It ice-cooled in the solution (60ml) of copper sulfate 5 hydrate (11.6g) and sodium chloride (14.3g), and the above-mentioned purple suspension was dropped. It ****(ed) at the room temperature after the end of dropping for further 3 hours. Extract a reaction solution by diethylether and saturation sodium bicarbonate solution neutralizes a diethyl ether layer. After the saturation sodium chloride aqueous solution's having washed and drying using anhydrous sodium sulfate, decompression distilling off of the solvent was carried out, and the 2-chloro 4-methoxy 7-methyl 1 and 3-benzothiazole (2.16g) were obtained.

subsequently -- dissolving the 2-chloro 4-methoxy 7-methyl 1 and 3-benzothiazole (2.16g) in methanol (50ml) -- sodium methoxide (5.48g) -- in addition, the heating reflux was carried out for 2 hours. Decompression distilling off of the solvent was carried out, the obtained oily matter was suspended in water, and it adjusted to pH 4 using acetic acid. This suspension was extracted by diethylether, saturation sodium bicarbonate solution neutralized the diethyl ether layer, the saturation sodium chloride aqueous solution washed, and it dried with anhydrous sodium sulfate. Decompression distilling off of the solvent was carried out, silica gel column chromatography refined, and 2, the 4-dimethoxy 7-methyl 1, and 3-benzothiazole (1.72g) were obtained.

^{1}H-NMR($CDCl_3$)

2.37(s, 3H, ArCH3-7), 3.98(s, 3H, OCH_3), 4.24(s, 3H, $ArOCH_3$), 6.78(d, J=7.9Hz, 1H, ArH-5), 6.96(d, J=7.9Hz, 1H, ArH-6)

MS ; [M^+] =209

(2) Synthesis of 2, 4-dimethoxy 1, and 3-benzothiazole 7-carboaldehyde (III) [2, the 4-dimethoxy 7-methyl 1 3-benzothiazole (1.72g), and cerium ammonium night REITO (20.8g) which were compounded above (1)] In addition to methanol (80ml), it ****(ed) for 5 minutes at 60 degrees C. Water was added to the oil which might be distilled off in the solvent, and it extracted by the methylene chloride. After the saturation sodium chloride aqueous solution's having washed the methylene chloride layer and drying with anhydrous sodium sulfate, the solvent was distilled off, silica gel column chromatography refined, and 2, 4-dimethoxy 1, and 3-benzothiazole 7-carboaldehyde (1.0g) were obtained.

^{1}H-NMR($CDCl_3$)

4.11(s, 3H, OCH_3), 4.27(s, 3H, $ArOCH_3$), 7.02(d, J=9Hz, 1H, ArH-5), 7.74(d, J=9Hz, 1H, ArH-6), 9.98(s, 1H, CHO)

MS ; [M^+] =223

(3) Synthesis of 2-amino 1-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-1-ethanol (V) [2, the 4-dimethoxy 1, and 3-benzothiazole 7-carboaldehyde (1.0g) which were compounded above (2)] It dissolved in the methylene chloride (30ml), a trimethylsilyl cyanide (2.4ml) and zinc iodide (290mg) were added, and it **** (ed) for 10 minutes at room temperature. The saturation sodium chloride aqueous solution washed reaction mixture, and the solvent was distilled off after drying with anhydrous sodium sulfate. The obtained oil was dissolved in tetrahydrofuran (30ml), and it cooled at 0 degree C. This was dropped at the tetrahydrofuran suspension (30ml) of lithium hydride aluminum (510mg). Sodium sulfate 10 hydrate was added after **** during 10 minutes at 0 degree C. After filtering reaction mixture by Celite, the solvent was distilled off, silica gel column chromatography refined, and 2-amino 1-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-1-ethanol (950mg) was obtained.

^{1}H-NMR(CD_3OD)

3.07(dd, J=9.7Hz, 12Hz, 1H, CH_2 NH_2), 3.14(dd, J=3.9Hz, 12Hz, 1H, CH_2 NH_2), 3.98(s, 3H, OCH_3), 4.19(s, 3H, $ArOCH_3$), 5.07(dd, J=9.7Hz, 3.9Hz, 1H, ArCHOH), 7.06(d, J=8.5Hz, 1H, ArH-5), 7.22(d, J=8.5Hz, 1H, ArH-6)

MS ; [M^+] =254

(4) 2-{[1- (t-butyl)-1 and 1-dimethylsilyl] oxy-}-2- 2, 4-dimethoxy 1, and (3-benzothiazole 7-IRU)-1-ethylamine (VI) synthesis [the 2-amino 1-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-1-ethanol (85mg) compounded above (3)] It suspended in the methylene chloride (3ml), lutidine (0.12ml) and trifluoro methanesulfonic acid t-butyldimethylsilyl (0.23ml) were added, and it ****(ed) at room temperature for 1 hour. Hydrochloric acid was added to 0 degree C bottom 1% of cooling, and ethyl acetate extracted. After drying an ethyl acetate layer with washing and anhydrous sodium sulfate in saturation sodium bicarbonate solution, Decompression distilling off of the solvent was carried out, silica gel column chromatography refined, and 2-{[1[1-(t-butyl)-1 and]-dimethylsilyl] Oxy-}-2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-1-ethylamine (62mg) was obtained.

^{1}H-NMR($CDCl_3$)

-0.11(s, 3H, Si CH_3), 0.07(s, 3H, Si CH_3), 0.90(s, 9H, SiC(CH_3)$_3$), 2.85 (dd, J=4.9Hz, 13Hz, 1H, CH_2NH2), 2.93(dd, J=6.7Hz, 13Hz, 1H, CH_2NH_2), 3.99(s, 3H, OCH_3), 4.23(s, 3H, ArOCH_3), 4.69(dd, J=4.9Hz, 6.7Hz, 1H, ArCHOTBS), 6.81 (d, J=7.9Hz, 1H, ArH-5), 7.04(d, J=7.9Hz, 1H, ArH-6)

(5) N1-[2-{[1-t-butyl-1 and 1-dimethylsilyl] oxy-}
- 2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU) ethyl]
- Synthesis of 2, 2, and 2-trifluoro acetamide (VII) [the 2-{[1-(t-butyl)-1 and 1-dimethylsilyl] oxy-}-2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-1-ethylamine (62mg) compounded above (4)] It dissolved in the pyridine (3ml), the anhydrous trifluoroacetic acid (72microl) was added, and it ****(ed) for 10 minutes at 0 degree C. Hydrochloric acid was added 1% and ethyl acetate extracted. After drying an ethyl acetate layer with washing and anhydrous sodium sulfate in saturation sodium bicarbonate solution, Carry out decompression distilling off and silica gel column chromatography refines a solvent. N1-[2-{[1[1-(t-butyl)-1 and]-dimethylsilyl] Oxy-}-2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU) ethyl]-2, 2, and 2-trifluoro acetamide (81mg) was obtained.

^{1}H-NMR($CDCl_3$)

-0.12(s, 3H, Si CH_3), 0.06(s, 3H, Si CH_3), 0.91(s, 9H, SiC(CH_3)$_3$), 3.46 (m, 1H, CH_2NHTFA), 3.69(m, 1H, CH_2NHTFA), 4.00(s, 3H, OCH_3), 4.24(s, 3H, ArOCH_3), 4.90(dd, J=4.3Hz, 8.6Hz, 1H, ArCHOTBS), 6.83(d, J=7.9Hz, 1H, ArH-5), 7.06(d, J=7.9Hz, 1H, ArH-6)

MS ;[M^+] =464

(6) synthesis of N1-[2-{[1[1-(t-butyl)-1 and]-dimethylsilyl] oxy-}-2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU) ethyl]-N1-methyl 2, 2, and 2-trifluoro acetamide (VIII) [N1-[2-{[1-(t-butyl)-1 and 1-dimethylsilyl] oxy-}-2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU) ethyl]-2, 2, and 2-trifluoro acetamide (81mg) compounded above (5)] It dissolved in N,N-dimethylformamide (3ml), sodium hydride (15mg) and a methyl iodide (25microl) were added, and it ****(ed) at 0 degree C for 1 hour. Water was added and ethyl acetate extracted. After a saturation sodium chloride aqueous solution's washing an ethyl acetate layer and drying with anhydrous sodium sulfate, Carry out decompression distilling off and silica gel column chromatography refines a solvent. N1-[2-{[1[1-(t-butyl)-1 and]-dimethylsilyl] Oxy-}-2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU) ethyl]-N1-methyl 2, 2, and 2-trifluoro acetamide (71mg) was obtained.

^{1}H-NMR($CDCl_3$)

-0.13(s, 3H, Si CH_3), 0.05(s, 3H, Si CH_3), 0.88(s, 9H, SiC $(CH_3)_3$), 2.99 (s, 3H, N(CH_3)TFA), 3.51(dd, J=7.9Hz, 13Hz, 1H, CH_2N(CH_3)TFA), 3.58(dd, J= 5.5, 13Hz, 1H, CH_2N(CH_3)TFA), 4.01(s, 3H, OCH_3), 4.25(s, 3H, ArOCH_3), 5.15 (dd, J=5.5Hz, 7.9Hz, 1HArCHOTBS), 6.82(d, J=8.6Hz, 1H, ArH-5), 7.05(d, J=8.6Hz, 1H, ArH-6)

MS ; [M^+] =478

(7) 1- 2, 4-dimethoxy 1, and (3-benzothiazole 7-IRU)-2-(methylamino)-synthesis of 1-ethanol (IX) 2-{[1[1-(t-butyl)-1 and]-dimethylsilyl] oxy-}-2- N1-[compounded above (6) -- Ethyl]-N1-methyl 2, 2, and 2-trifluoro acetamide (337mg) is dissolved in tetrahydrofuran (10ml). (2, 4-dimethoxy 1, 3-benzothiazole 7-IRU) The tetrahydrofuran 1.0 molar solution (1.1ml) of fluoridation tetrabutylammonium was added, and it ****(ed) for 20 minutes at 0 degree C. Water was added and ethyl acetate extracted. A saturation sodium chloride aqueous solution washes an ethyl acetate layer, after drying with anhydrous sodium sulfate, decompression distilling off of the solvent is carried out, and silica gel column chromatography refines, and it is N1-[2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-2-hydroxyethyl].
- the N1-methyl 2 and 2 -- 2-trifluoro acetamide (238mg) obtained.
N1-[2-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-2-hydroxyethyl]-N1-methyl [which was compounded above] 2, 2, and 2-trifluoro acetamide (45mg) is dissolved in methanol (5ml). Sodium methoxide (70mg) was added and it ****(ed) for 40 minutes at room temperature. After carrying out decompression distilling off of the solvent, alumina column chromatography refined and 1-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-2-(methylamino)-1-ethanol (23mg) was obtained.

^{1}H-NMR(CD_3OD)

2.41(s, 3H, $NHCH_3$), 2.72(dd, J=4.3Hz, 12Hz, 1H, CH_2NHCH_3), 2.83(dd, J=9.2Hz, 12Hz, 1H, CH_2NHCH_3), 3.96(s, 3H, OCH_3), 4.18(s, 3H, ArOCH_3), 4.90(dd, J=4. 3Hz, 9.2Hz, 1H, Ar $CHOHCH_2$), 6.93(d, J=7.9Hz, 1H, ArH-5), 7.12(d, J=7.9Hz, 1H, A rH-6)

(8) Synthesis of 4-hydroxy 7-[1-hydroxy 2-methylamino ethyl]-1 and 3-benzothiazole 2(3H)-ON (I) 1-(2, 4-dimethoxy 1, 3-benzothiazole 7-IRU)-2- compounded above (7) (Methylamino) -1-ethanol (23mg) was suspended in the methylene chloride, the methylene chloride solution (1.2ml) of boron tribromide was added, and it agitated at room temperature for 36 hours. After having added bicarbonate of soda, neutralizing and condensing, fractionation was carried out by making the obtained concentrate into an eluent with the liquid high speed chromatography using the ODS column (YMC CO., LTD., SH-343-7) as 10% methanol

90%20mM potassium phosphate buffer solution (pH 7.0) and a column. After freeze-drying an activity fraction, methylene chloride methanol (1:1) extracted and 1.66mg of 4-hydroxy 7-[1-hydroxy 2-methylamino ethyl]-1 and 3-benzothiazole 2(3H)-ON orthophosphates were obtained.

^{1}H-NMR(D_2O)

2.57(s, 3H, $NHCH_3$), 3.09(dd, J=4.3Hz, 13Hz, 1H, CH_2NHCH_3), 3.15(dd, J=9.2Hz, 13Hz, 1H, CH_2NHCH_3), 4.8 (dd, J=4.3Hz, 9.2Hz, 1H, $CHOHNHCH_3$), 6.5(d, J=8.6Hz, 1H, ArH-5), 6.8(d, J=8.6Hz, 1H, ArH-6)

Melting point: About 180 degrees C (decomposition)

Example 1 of a pharmacological test Extraction guinea pig bronchial tube relaxation operation examination Production of the guinea pig bronchial tube specimen was performed according to the procedure of Akepsilonasu (Akepsilonasu, J.Pharma.Pharmacol.vol.4, pp671 (1962)). The cervix of a guinea pig and muscles were cut open along the median line, the cervical trachea until it results in a thorax from a mouth epiglottic cartilage inferior extremity was taken out, and it dipped into tie load HEPES buffer solution (nutrient solution). After covering with the filter paper fully soaked in the nutrient solution in the petri dish and removing the loose connective tissue of an outer membrane on it, it was made the ring of two to 3 mm width, with the cartilago attached. The cartilago by the side of the opposite of a muscle was opened with scissors, and three pieces were mutually connected using adhesives, respectively, and it was considered as the specimen, and hung in the Magnus equipment under 37 degrees C, CO25%, and O295% of conditions. Fixing the inferior extremity of the specimen, the superior extremity was connected with the transducer for tension measurement (Nihon Kohden, TB-611T), was distorted and recorded the tension (relaxation) on isometric property using the amplifier for pressure (Nihon Kohden, AP-621G).

The compound and contrast compound of the example 2 were prescribed for the patient by the concentration shown in drawing 3 more cumulatively than low concentration, and the concentration dependence curve of the tension (relaxation) of a specimen to a medicine was drawn. Moreover, from that concentration dependence curve, it asked for the concentration (molarity) of the sample offering compound corresponding to tension (relaxation) 50%, and the negative opposite numerical value of this figure was made into pD2 value.

The result was as being shown in drawing 3 . In a guinea pig bronchial tube, [4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2(3H)-ON] It had an about 1800 times of the salbutamol which is a well-known compound, and about 4000 times as many, very strong bronchodilator action as isoproterenol.

Example 2 of a pharmacological test beta2 receptor selectivity examination The cervix of a guinea pig and muscles were cut open along the median line, the heart was extracted, and the left artium was started. Like the example 1 of a pharmacological test, the inferior extremity of the specimen was fixed, and the superior extremity was connected with the transducer for tension measurement (Nihon Kohden, TB-611T), and measured change of the heart rate using the amplifier for heart rate measurement (Nihon Kohden, AT-601G). It asked for the maximal heart rate of isoproterenol first, and it was made into 100%. The compound and contrast compound of the example 2 were prescribed for the patient more cumulatively than low concentration, and the concentration dependence curve of the heart rate of a specimen to a medicine was drawn. From that concentration dependence curve, it asked for the concentration (molarity) of the sample

offering compound corresponding to reinforcement 50%, and the negative opposite numerical value of this figure was made into pD2 value.
Moreover, together with the result of the example 1 of a pharmacological test, the selectivity over beta2 receptor of a test drug was searched for by the following formulas.
Selectivity = 10 (pD2 of the pD2-left-artium heart rate potentiation of a bronchial tube relaxation operation)
The result was as being shown in Table 1.

表 1

試験化合物	pD2値		選択性
	気管 (β2受容体)	左心房 (β1受容体)	気管／左心房(倍)
実施例2の化合物	10.77	6.75	10471
フォルモテロール	10.60	8.02	380
サルブタモール	7.50	6.78	5.25
イソプロテレノール	7.17	7.97	0.16

4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]
- 1 and 3-benzothiazole 2(3H)-ON had very weak heart rate potentiation.
Moreover, 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2(3H)-ON had the about 2000 times of the salbutamol of a well-known compound, and about 30 times as much, extremely excellent alternative beta2 receptor stimulation as FORUMO Taylor.
Example 3 of a pharmacological test Retention time examination of an extraction guinea pig bronchial tube relaxation operation [the retention time examination of the bronchial tube relaxation operation using a guinea pig bronchial tube] It carried out according to the procedure of Voss and others (Voss et al., Euro.J. Pharmacol.Vol.227, pp 403-409 (1992)). According to the procedure of the example 1 of a pharmacological test, the guinea pig bronchial tube was hung to equipment. The maximum contraction was guided using the 3x10-5M mesa choline, and this was made into 0% of the relaxation rate. Salbutamol and isoproterenol were prescribed for the patient so that it might be set to 3x10-7M, the maximum relaxation was guided, and this was made into 100% of the relaxation rate so that the compound of an example 2 and FORUMO Taylor might be set to 1x10-8M. Tie load HEPES buffer solution washed the guinea pig bronchial tube immediately after guiding the maximum relaxation, and contraction was temporally measured for this time as reaction time of onset.
The result was as being shown in drawing 4 . [4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-2 of this invention, 3-dihydro1, and 3-benzothiazole 2-ON] When the half-life of activity compared, it is about 0.58 time of isoproterenol of a well-known compound, about 0.12 time of salbutamol, and about 0.09 time FORUMO Taylor, and had beta2 receptor stimulation with very short reaction time.
Example 4 of a pharmacological test Depressant action (1) to the bronchoconstriction reaction by the acetylcholine of the bottom mouse of anesthesia Measurement of respiratory tract contraction measured

change of airway resistance using determination-of-airway-resistance equipment according to the Konzett-Rossler method. It is PENTO barbitone sodium in the abdominal cavity of a mouse. After injecting kg in 100mg /and anesthetizing, the tracheotomy was carried out, glass tracheal cannulae were intubated, and 60 mechanical ventilation was performed in the 1-time air-flow rate of 0.6ml, and 1 minute using the close nature animal respirator (harbored APARATASU, 683 type). It is a pancuronium star's picture after the completion of an operation. kg was intravenously injected in 0.1mg /, and spontaneous respiration was stopped. ** of the air overflowed from the side shoot of a tracheal cannula was measured with the ** transducer (UGO basil, 7020 type), and this was made into the index of a respiratory tract contraction reaction. The compound of an example 2, FORUMO Taylor, and salbutamol were administered intravenously just before administering acetylcholine intravenously.

The result was as being shown in drawing 5 . 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1, 3-benzothiazole 2 (3H)

- ON had a very strong bronchodilator action.

Example 5 of a pharmacological test Degranulation inhibition test from a Homo sapiens mast cell The depressant action to the degranulation from a Homo sapiens mast cell was measured. The Homo sapiens mast cell was obtained from Homo sapiens ****** by cultivation according to the procedure (Yanagida et al., Blood, 86 volumes, 3705 pages, 1995) of Yanagida and others. Homo sapiens IgE was added so that the last concentration might come in ml and 1microg /into cell culture liquid, it cultivated for 1 hour or more, and sensitization was carried out. It suspended in [after washing a cell] tie load HEPES buffer solution, and it poured distributively on the plate so that it might be set to 2x104 pieces / well. Furthermore, it added so that it might become the concentration as which the last concentration was displayed, and the compound of the example 2 was cultivated for 30 minutes. Next, culture supernatants were collected after having added the anti human IgE immune body so that the last concentration might become in ml and 3microg /, and cultivating for 30 minutes. The rate of degranulation made the index bird PUTAZE activity included in a supernatant, and it asked for it. That is, the substrate liquid (0.8mM benzoyl DL-arginine p-nitroanilide) of 100microl was added to the supernatant of 50microl, it put gently at 37 degrees C, and the absorbance of 405nm was measured. Moreover, the cell was crushed in the try ton X-100 0.2%, the supernatant was diluted gradually, bird PUTAZE activity was measured about each diluent, and the standard curve was created. The rate of degranulation was computed from the standard curve using the bird PUTAZE activity in the supernatant obtained from the cell to which the study drug was made to react.

The result was as being shown in drawing 6 . 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1, 3-benzothiazole 2 (3H)

- ON had the outstanding Homo sapiens mast-cell-degranulation depressant action.

Example 6 of a pharmacological test TNF-alpha production inhibition test from a Homo sapiens mast cell The depressant action to the TNF-alpha production from a Homo sapiens mast cell was measured. A Homo sapiens mast cell is the procedure (Yanagida et al., Blood, 86 volumes, 3705 pages, 1995) of Yanagida and others.

It was alike, and it applied correspondingly and obtained from Homo sapiens cord blood by cultivation. Homo sapiens IgE was added so that the last concentration might come in ml and 1microg /into cell culture liquid, it cultivated for 1 hour or more, and sensitization was carried out. It suspended in [after washing a cell] the medium, and it poured distributively on the plate so that it might be set to 4x105 pieces / well. Furthermore, it added so that it might become the concentration as which the last concentration was displayed, and the compound of the example 2 was cultivated for 30 minutes. Next, culture supernatants were collected after having added the anti human IgE immune body so that the last concentration might become in ml and 3microg /, and cultivating for 6 hours. The quantity of TNF-alpha in a supernatant was

measured by the ELISA method (a bio-source company, Cytoscreen Immunoassay Kit).
The result was as being shown in drawing 7 . 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1, 3-benzothiazole 2 (3H)
- ON had the outstanding TNF-alpha production depressant action.
The test result of the example 1-6 of a pharmacological test is as being shown in Table 2.

表 2

試験	試験化合物			
	実施例2の化合物	フォルモテロール	サルブタモール	イソプロテレノール
気管支弛緩作用	pD2＝10．77	pD2＝10．60	pD2＝7．50	pD2＝7．17
選択性（倍）	10471	380	5．25	0．16
気管支弛緩作用持続時間	4（分）	48（分）	37（分）	7（分）
気管支弛緩作用（in vivo）（ED_{50}）	2μg／kg以下	1～10μg／kg	10～100μg／kg	実施せず
TNF-α産生抑制（培養細胞）	IC50＝0．52（nM）	実施せず	実施せず	実施せず
IL-4産生抑制	IC50＝0．1（nM）	実施せず	実施せず	実施せず

薬理試	(1)モルモット気管支筋	(2)β2／β1選択性（	(3)モルモット気管弛緩	(4)マウス気管支弛緩作	(5)肥満細胞脱顆粒抑制	(6)肥満細胞ＴＮＦ－α

Example 7 of a pharmacological test Depressant action (2) to the bronchoconstriction reaction by the acetylcholine of the bottom mouse of anesthesia Measurement of respiratory tract contraction was performed like the example 4 of a pharmacological test. The compound and FORUMO Taylor who compounded by the same procedure as an example 2 administered intravenously, just before administering the first acetylcholine intravenously. The acetylcholine which double-******(ed) was prescribed for the patient from low concentration, the concentration dependence curve to acetylcholine was drawn, and it asked for the area under the curve.

The result was as being shown in Table 3. 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1, 3-benzothiazole 2 (3H)

- ON had a strong bronchodilator action as compared with FORUMO Taylor.

表 3

被験化合物	n	用量 μg／kg	曲線下面積 (%・μg／kg) mean± S. E.	抑制率 (%)
対照群	7	—	19.0 ± 3.2	—
実施例２の化合物	7	2	8.9 ± 2.2 *	53
実施例２の化合物	7	5	5.1 ± 0.7 **	73
フォルモテロール	7	2	12.0 ± 2.0	37
フォルモテロール	7	5	9.8 ± 2.6 *	48

＊：Ｐ＜０．０５，　＊＊：Ｐ＜ ０．０１は対照群に対する有意差を示す。

Example 8 of a pharmacological test Depressant action to the skin reaction by the passive cutaneous anaphylaxis and histamine of a mouse [the skin reaction by the passive cutaneous anaphylaxis and histamine of a mouse] It carried out according to the procedure of Inagaki and others (Inagaki et al., Int.Arch.Allergy Appl.Immunol.Vol.87, pp 254-259 (1988)). 10micro of 20microg/ml mouse anti-dinitrophenyl monoclonal IgE immune bodies l were injected into the mouse right ear under anesthesia. 2x10 to 4 g/ml histamine 10microl was again injected into the mouse left ear under anesthesia 48 hours afterward. Immediately after that, intravenous injection of 0.25ml of the physiological salines containing 0.25mg of dinitrophenyl-ized

cow serum albumins and 1.25mg of Evans Blue pigments was carried out, and the reaction was caused. After separating the reactive site after 30 minutes and carrying out incubation at 37 degrees C with 0.35ml of 1N potassium hydroxides overnight, by mixing with 4.65ml of acetone phosphoric acid mixture (13:5), the pigment was extracted and absorbance with a wavelength of 620nm was measured. The compound and salbutamol which were compounded by the same procedure as an example 2 were administered intravenously just before histamine intradermal injection.

The result which receives the skin reaction by passive cutaneous anaphylaxis and histamine was as being shown in Table 4 and 5, respectively. 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2(3H)-ON had very strong blood-vessel-permeability sthenia depressant action as compared with the salbutamol of a well-known compound.

表 4

被験化合物	n	用量 μg／kg	漏出色素量 (μg) mean ±S.E.	抑制率 (%)
対照群	6	−	10.0 ± 1.4	−
実施例２の化合物	6	0．3	9.1 ± 0.6	9
実施例２の化合物	6	1	6.2 ± 0.2 *	38
実施例２の化合物	6	3	4.2 ± 0.4 **	58
サルブタモール	6	0．3	10.0 ± 1.3	0
サルブタモール	6	1	12.4 ± 1.0	−24
サルブタモール	6	3	11.2 ± 1.4	−12

*：P＜0.05，　**：P＜ 0.01は対照群に対する有意差を示す。

表 5

被験化合物	n	用量 μg／kg	漏出色素量 (μg) mean ±S.E.	抑制率 (%)
対照群	6	−	8.3 ± 1.5	−
実施例２の化合物	6	0．3	4.7 ± 0.3	43
実施例２の化合物	6	1	4.1 ± 1.0 *	51
実施例２の化合物	6	3	2.7 ± 0.2 *	67
サルブタモール	6	0．3	7.3 ± 1.2	12
サルブタモール	6	1	7.5 ± 0.9	10
サルブタモール	6	3	6.8 ± 0.8	18

＊：Ｐ＜０．０５は対照群に対する有意差を示す。

Example 9 of a pharmacological test Depressant action to the skin reaction by the passive cutaneous anaphylaxis and the chemical mediator of a rat [the skin reaction by the passive cutaneous anaphylaxis and the chemical mediator of a rat] It carried out according to the procedure of Eda and others (Eda et al., Int. Arch.Allergy Appl.Immunol.Vol.92, pp 209-216 (1990)). Every three right and left and a total of six reactive sites were set as the rat regions-of-back skin which carried out hair cutting across the median line under anesthesia. 0.1ml of physiological salines were made the 1st point, and intradermal injection of 0.1ml of the 200 ng(s)/ml mouse anti-dinitrophenyl monoclonal IgE immune bodies was carried out to the 2nd point as a contrast part of passive cutaneous anaphylaxis, respectively. To the 3rd point, in 48 hours, as a contrast part of the skin reaction by a chemical mediator under anesthesia again [0.1ml of physiological salines] 5x10 to 7 g/ml serotonin 0.1ml was made the 5th point, and intradermal injection of 0.1ml of the 3x10 to 7 g/ml platelet activating factors was carried out for 2x10 to 5 g/ml histamine 0.1ml to the 6th point at the 4th point, respectively. Subsequently, intravenous injection of 1ml of the physiological salines containing 1mg of dinitrophenyl-ized cow serum albumins (DNP-BSA) and 5mg of Evans Blue pigments was carried out, and the reaction was caused. After separating the reactive site after 30 minutes and carrying out incubation at 37 degrees C with 1ml of 1N potassium hydroxides overnight, by mixing with 8.3ml of acetone phosphoric acid mixture (13:5), the pigment was extracted and absorbance with a wavelength of 620nm was measured. The compound and salbutamol which were compounded by the same procedure as an example 2 were administered intravenously just before chemical mediator intradermal injection.

The result was as being shown in Table 6. 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1, 3-benzothiazole 2 (3H)

- ON had very strong blood-vessel-permeability sthenia depressant action as compared with salbutamol.

化合物	抑制率 (%)
	1
	29
	59
	45

表 6

被験化合物	n	用量	受動皮膚アナフィラキシー		ヒスタミン		セロトニン		血小板活性化因	
		μg/kg	色素量 (μg)	抑制率 (%)	色素量 (μg)	抑制率 (%)	色素量 (μg)	抑制率 (%)	色素量 (μg)	抑 (
対照群	6	−	89.8±10.5	−	51.6±2.4	−	62.4±3.8	−	43.9±4.5	
実施例２の化合物	6	0．1	69.0±15.7	23	58.2±4.3	-13	70.8±3.8	-13	43.3±2.0	
実施例２の化合物	6	1	19.6± 5.6 **	78	40.2±3.4 *	22	36.8±2.7 **	41	30.9±4.9 **	
実施例２の化合物	6	１０	6.8± 1.4 **	92	26.0±1.3 **	50	12.0±1.8 **	81	17.8±2.2 **	
サルブタモール	6	１０	18.9± 4.8 **	78	41.7±3.8	19	50.0±3.0	20	24.3±3.2 **	

＊：Ｐ＜０．０５、＊＊：Ｐ＜０．０１は対照群に対する有意差を示す。

Example 10 of a pharmacological test Depressant action to the respiratory tract contraction reaction by ascaris extract inhalation of the bottom guinea pig of awakening The respiratory tract contraction reaction by ascaris extract inhalation was performed according to the procedure of Inoue and others (Inoue et al., ASTHMA Vol 4, pp 74-79 (1991)). Intraperitoneal injection of 20micro of ascaris extractants g and the silica gel 20mg was carried out to the guinea pig twice [a total of] at intervals of two weeks, and sensitization was carried out to it.

From the one-week back of the last sensitization, ascaris extract was inhaled for 1 minute using the ultrasonic nebulizer (OMRON, NE-U07 type) at intervals of one week a total of 2 times and 0.1%, and the respiratory tract contraction reaction was caused. The normal group inhaled the physiological saline instead of ascaris extract. Measurement of respiratory tract contraction was measured using the breathing resistance and the airway hyperreactivity measurement system for a mite experiment (a chest, animal ASUTO TMC-2100). The head was taken out, the guinea pig was put in in the body chamber, the oral cavity and a nasal cavity were covered with the mask of the conus form, it connected with amplifier through the differential pressure transducer, and respiratory flux was calculated. Moreover, the 30Hz sine wave was given to the body surface using the speaker and the generator, the atmospheric pressure in a body chamber was connected to amplifier through the differential pressure transducer, and the pressure change in a chamber was determined. Breathing resistance was automatically computed by computer analysis using the formula of Hyatt from this pressure change and 30Hz minute air current change which ****(ed) to ventilation. In front of the dichotomy of ascaris extract inhalation, the compound and salbutamol which were compounded by the same procedure as an example 2 used 10 ** type nebulizer (a chest, animal ASUTO TMC-2100), and carried out inhalation medication for 1 minute. It asked for the pace of decrease after ascaris extract inhalation of respiratory flux, and the rate of increase after ascaris extract inhalation of breathing resistance by the following formulas.

The pace of decrease of respiratory flux (%) -- respiratory flux B: before =[(A-B) /A] x100A:test compound inhalation -- breathing resistance 3 minutes after rate-of-increase (%) =[(B' - A') /A'] x100A 'breathing resistance B before :test compound inhalation':ascaris extract inhalation of the respiratory flux breathing resistance 3 minutes after ascaris extract inhalation The result was as being shown in Table 7 and 8. 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1 and 3-benzothiazole 2(3H)-ON had a strong bronchodilator action as compared with salbutamol.

表 7

被験化合物	n	用 量 μg／ml	呼吸流量 (% 減少率) mean± S. E.	抑制率 (%)
正常群	12	−	9.1 ± 3.8 *	−
対照群	12	−	40.9 ± 6.1	−
実施例２の化合物	12	３０	8.4 ± 7.8 **	９９
サルブタモール	12	３０	17.3 ± 6.3	７２

＊：Ｐ＜０．０５、＊＊：　Ｐ＜０．０１は対照群に対する有意差を示す。

表 8

被験化合物	n	用 量 μg／ml	呼吸抵抗 (% 増加率) mean± S. E.	抑制率 (%)
正常群	12	−	18.4 ± 7.3 **	−
対照群	12	−	49.8 ± 8.5	−
実施例２の化合物	12	３０	15.6 ± 4.3 **	１００
サルブタモール	12	３０	24.8 ± 5.8 *	８０

＊：Ｐ＜０．０５、＊＊：　Ｐ＜０．０１は対照群に対する有意差を示す。

the example 11 of a pharmacological test -- a normal guinea pig -- 0.5% of acetylcholine -- 10 ** type nebulizer Depressant action to the respiratory tract contraction reaction by acetylcholine inhalation of the bottom guinea pig of awakening (a chest --) The respiratory tract contraction reaction was caused by inhaling for 1 minute using animal ASUTO TMC-2100. Measurement of respiratory tract contraction was performed like the example 10 of a pharmacological test. The compound and salbutamol which compounded the respiratory tract contraction by acetylcholine by the same procedure as a twice deed and an example 2 with about 3 time intervals used 10 ** type nebulizer (a chest, animal ASUTO TMC-2100), and carried out inhalation medication for 1 minute just before acetylcholine inhalation of eye twice. The control activity of the test compound to the respiratory tract contraction reaction by acetylcholine inhalation was searched for by the following formulas.

The pace of decrease B of the respiratory flux after acetylcholine inhalation of the respiratory-tract

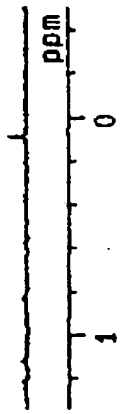
contraction reaction by acetylcholine inhalation of control activity (%) =[(A-B) /A] x100A:1 time: Pace of decrease of the respiratory flux after acetylcholine inhalation of eye twice The result was as being shown in Table 9. 4-hydroxy 7-[1-(1-hydroxy 2-methylamino) ethyl]-1, 3-benzothiazole 2 (3H)
- ON had a very strong bronchodilator action as compared with salbutamol.

表 9

被験化合物	n	用量 μg／ml	呼吸流量 (%) mean±S.E.	抑制率 (%)
対照群	10	−	10.1 ± 8.3	−
実施例２の化合物	10	1	26.1 ± 7.4	１８
実施例２の化合物	10	3	35.7 ±13.3	２８
実施例２の化合物	10	１０	57.1 ± 9.5 **	５２
実施例２の化合物	10	３０	75.6 ±10.5 **	７３
対照群	8	−	13.1 ±12.2	−
サルブタモール	8	１０	14.9 ±17.1	２
サルブタモール	8	３０	56.5 ±13.6	５０
サルブタモール	8	１００	69.9 ±11.1 *	６５

＊：Ｐ＜０．０５、＊＊：　Ｐ＜０．０１は対照群に対する有意差を示す。

[Drawing 1]



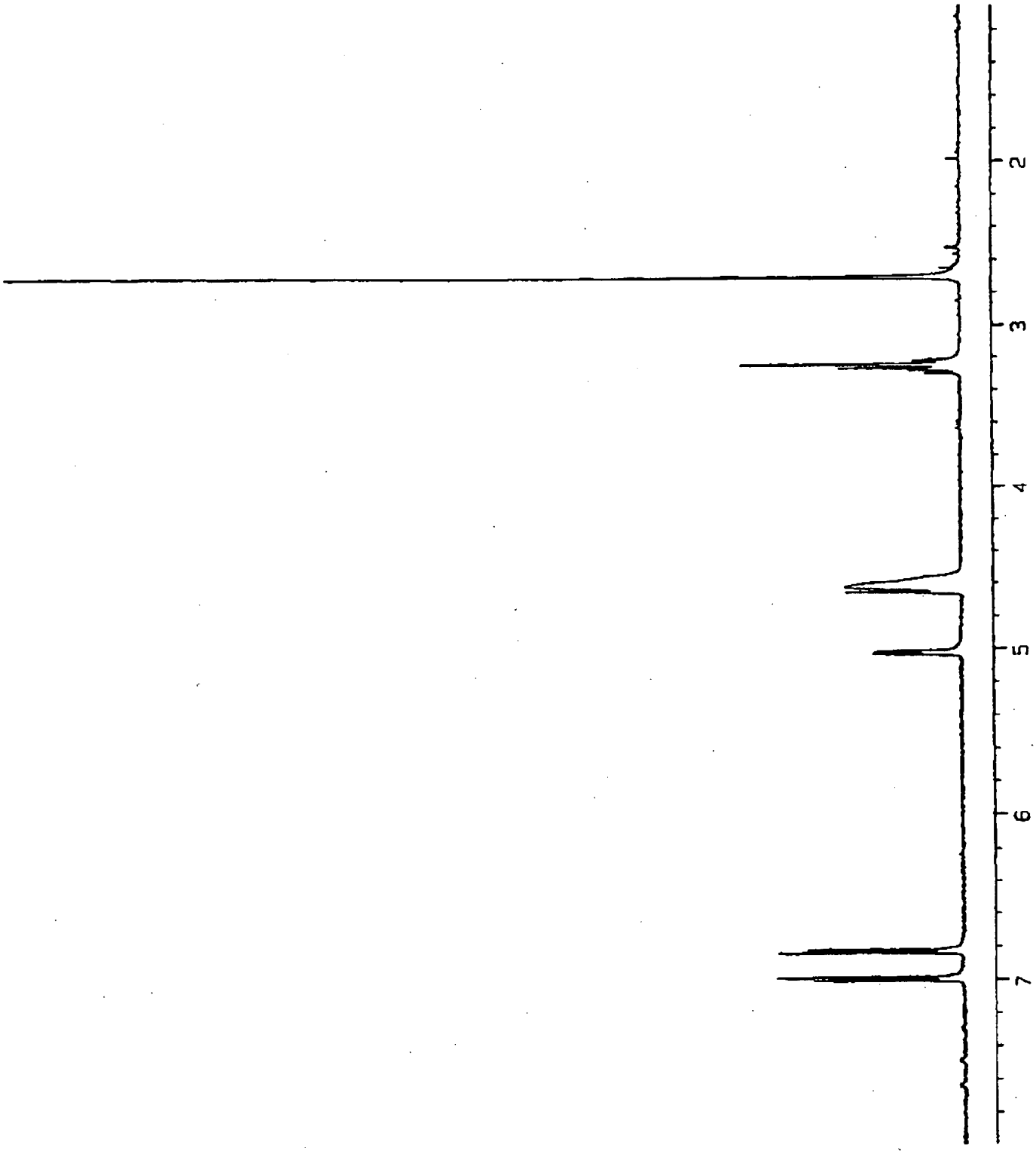
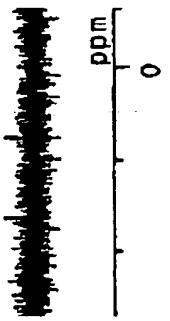


FIG. 1

[Drawing 2]



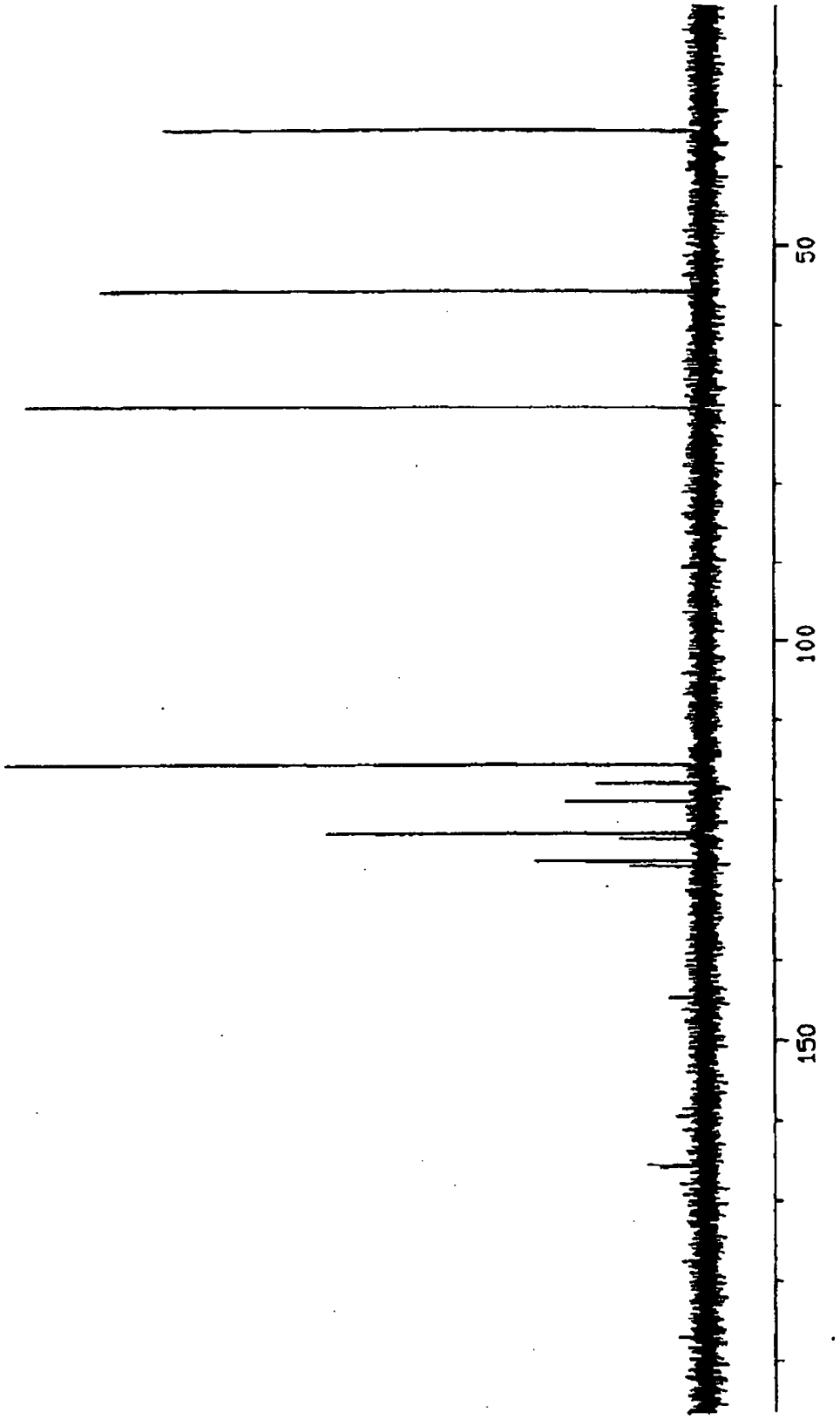


FIG. 2

[Drawing 3]

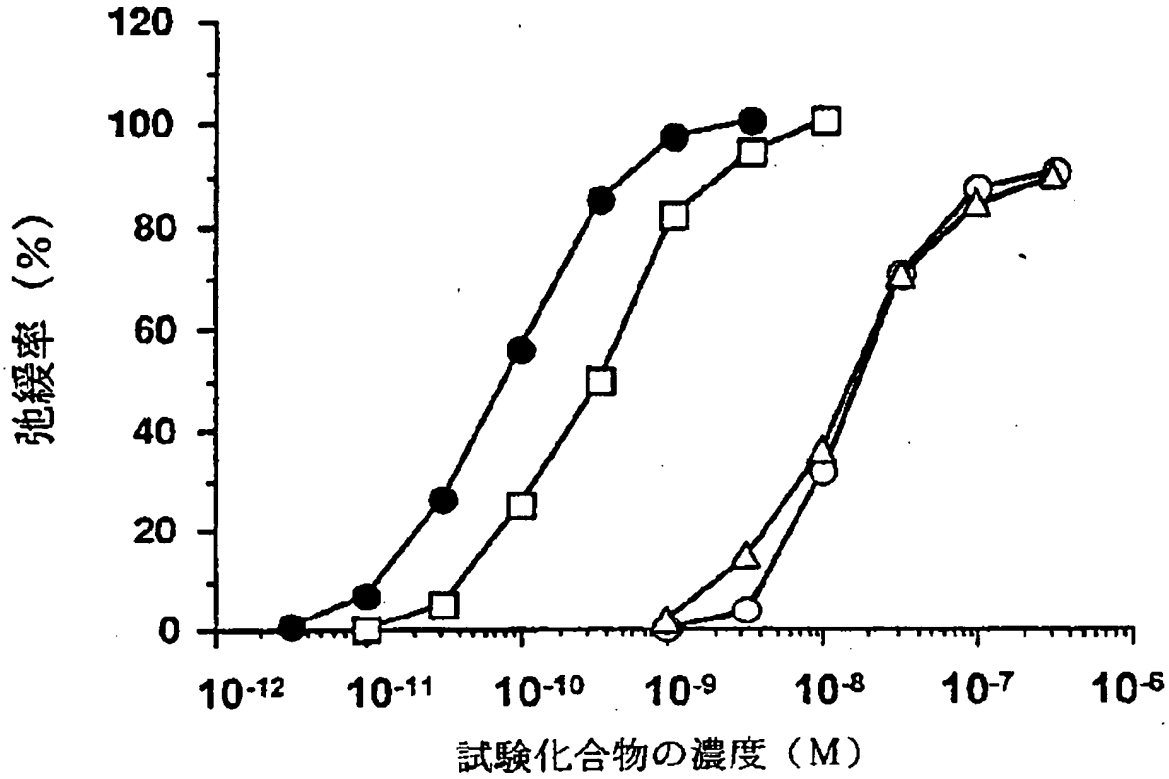


FIG. 3

[Drawing 4]

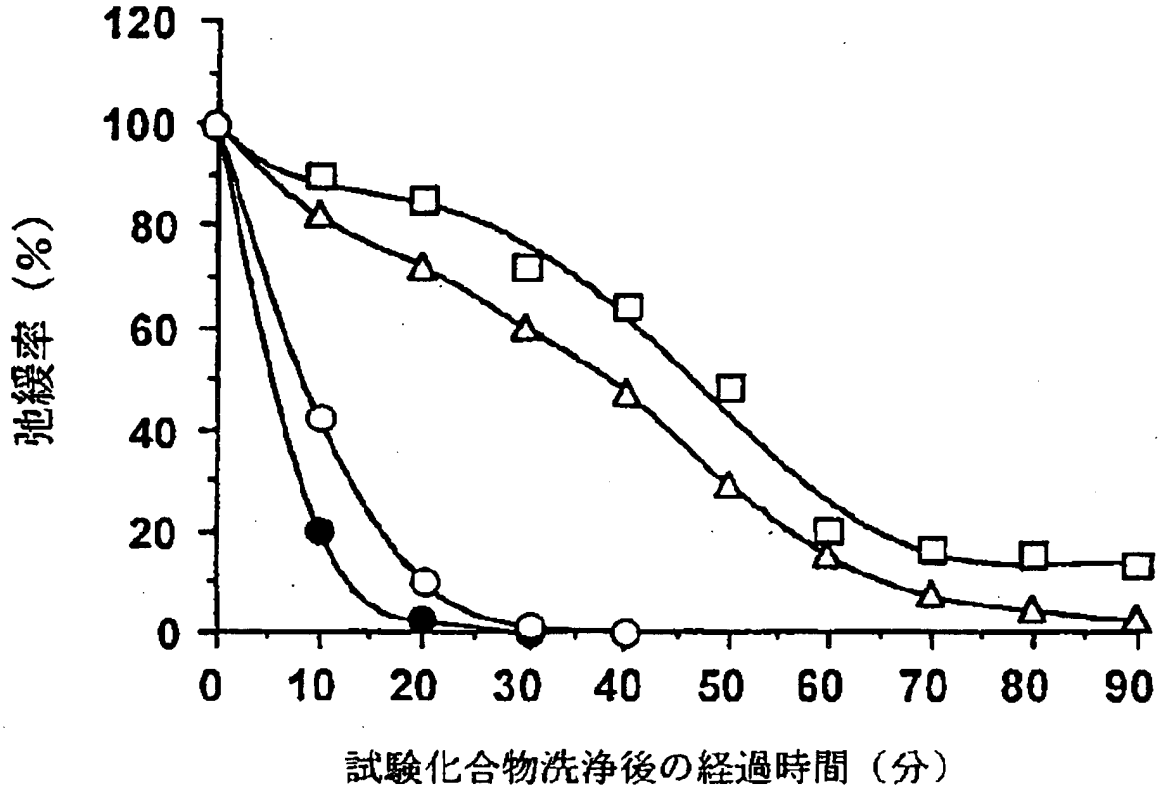


FIG. 4

[Drawing 5]

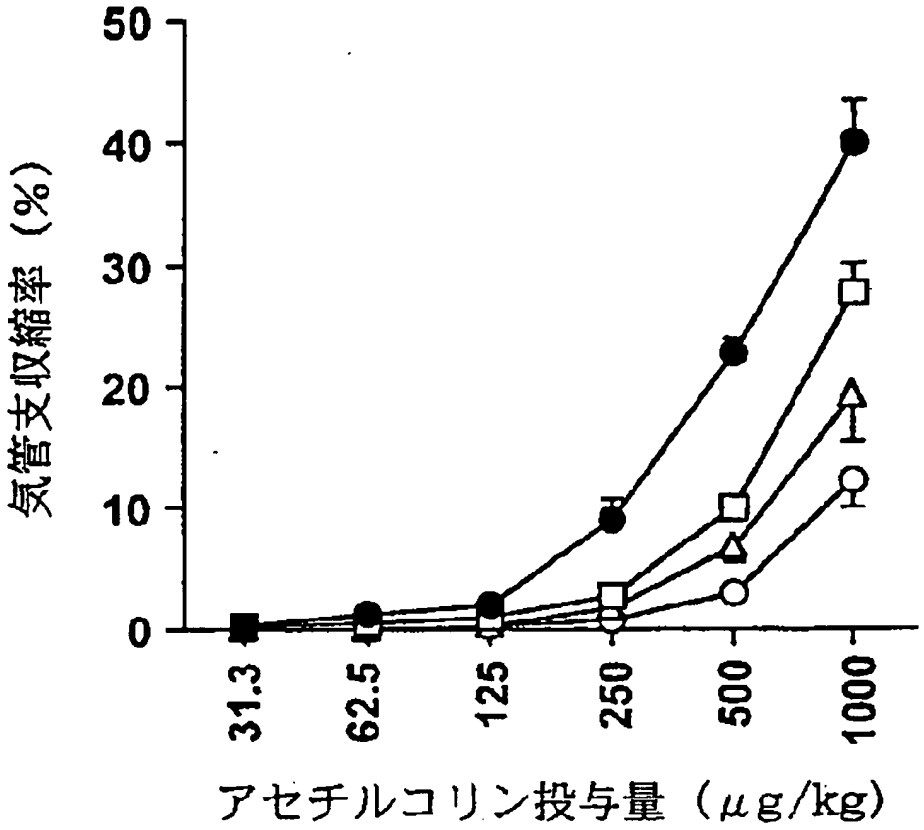


FIG. 5

[Drawing 6]

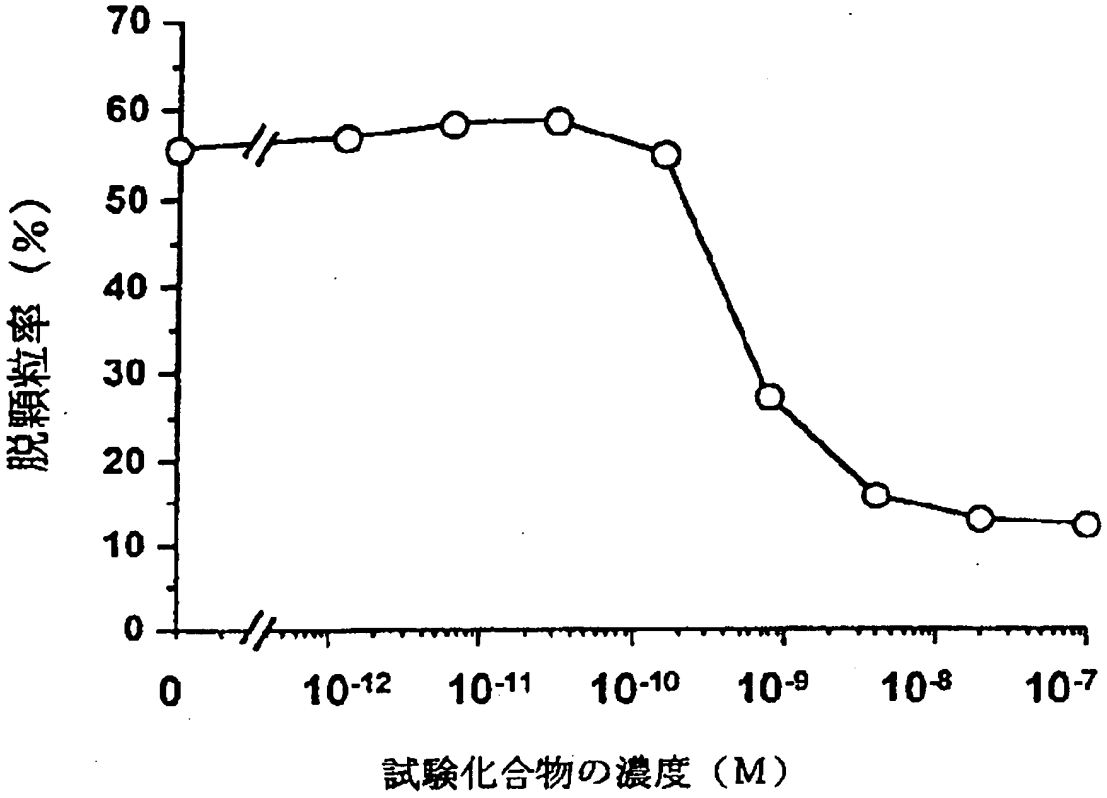


FIG. 6

[Drawing 7]

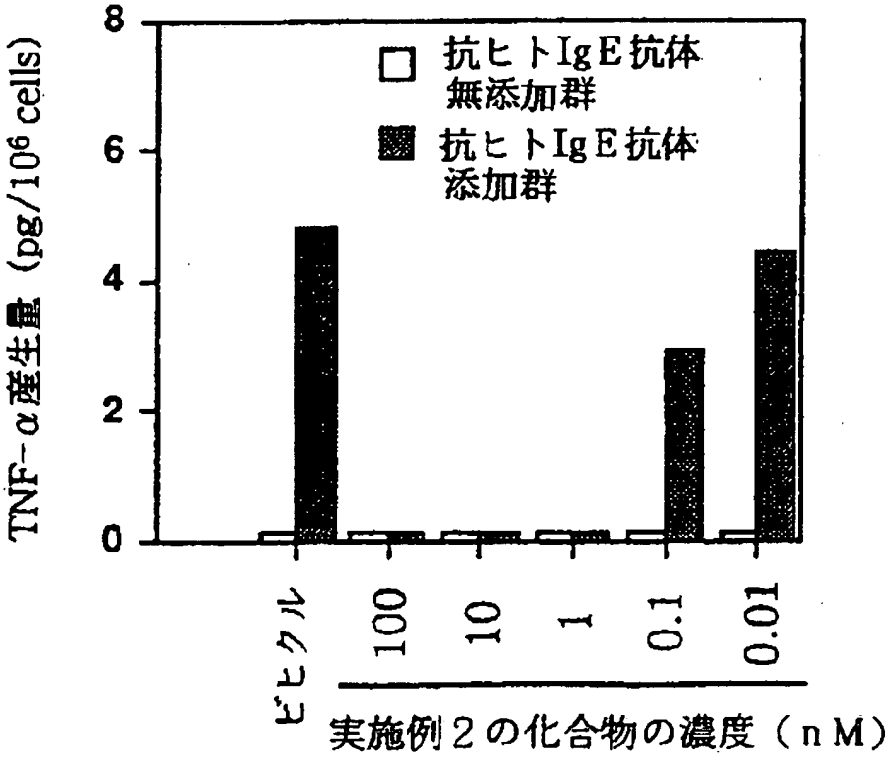


FIG. 7

[Drawing 8]

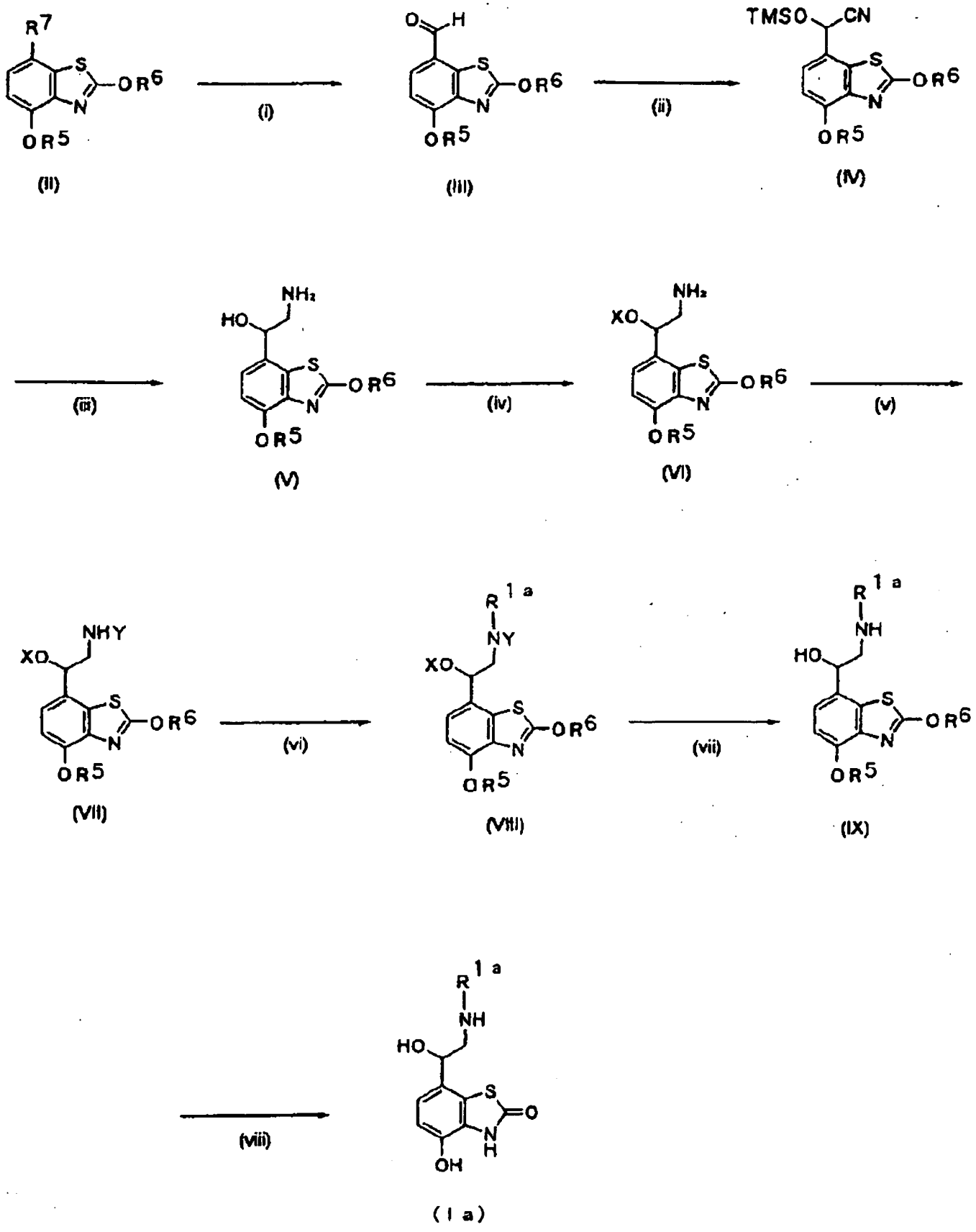


FIG. 8

FIG. 8

[Translation done.]